Drug Class Review

Miscellaneous and Serotonergic Agents

28:16.04.92 Antidepressants, Miscellaneous
Bupropion (Wellbutrin®; Wellbutrin® SR; Wellbutrin® XL; Zyban®)
Mirtazapine (Remeron®; Remeron® SolTab™)

28:16.04.24 Serotonin Modulators
Nefazodone (Serzone®)
Trazodone (Desyrel®)
Vilazodone (Viibryd®)
Vortioxetine (Trintellix®)

28:92 Central Nervous System Agents, Miscellaneous
Atomoxetine (Strattera®)

28:28 Antimanic Agents
Lithium (Eskalith CR®; Eskalith®; Lithobid® Slow-release)

Final Report
August 2016

Review prepared by:
Melissa Archer, PharmD, Clinical Pharmacist
Carin Steinvoort, PharmD, Clinical Pharmacist
Vicki Frydrych, PharmD, Clinical Pharmacist
Joanne LaFleur PharmD, MSPH, Associate Professor
Gary Oderda, PharmD, MPH, Professor

University of Utah College of Pharmacy

Contents

Executive Summary

Introduction:

The first antidepressant was discovered in the 1950s while researching treatments for schizophrenia. Some of the earliest had a three-ring chemical structure, tricyclic antidepressants (TCAs). These agents were effective with significant adverse events. Newer agents were developed to target specific receptors with improved safety profiles. This report focuses on miscellaneous and serotonergic modulators (atomoxetine, bupropion, lithium, mirtazapine, nefazodone, trazodone, vilazodone and vortioxetine) which are labeled for use in mental health disorders (depression, bipolar disorder, attention deficit hyperactivity disorder (ADHD), seasonal affective disorder and smoking cessation. All of the miscellaneous agents are available in oral tablet or capsule formulations.

Clinical guidelines for the treatment of depression recommend Cognitive Behavioral Therapy (CBT) for all patients. Recommendations for first-line pharmacotherapy involve use of a second-generation antidepressant. Patients who are partial responders at 6-8 weeks, should receive an alternative antidepressant, a combination of antidepressant agents or adjunctive treatment with another class of medications including lithium, thyroid hormone, atypical antipsychotic agent or dopamine agonist. Non-responders should be referred to a specialist. Medication therapy should be adjusted until full remission is achieved and treatment continued for an additional 6-9 months to prevent relapse. Chronic maintenance therapy is recommended in patients with two or more episodes of depression. Clinical guidelines for the treatment of bipolar disorder recommend medication therapy for acute manic episodes using mood stabilizers, anticonvulsants or antipsychotic agents. Medication therapy should be continued until full remission is achieved and combination therapy is recommended in patients with treatment-resistance to a single agent. Clinical guidelines for the treatment of ADHD recommend treatment of preschool children with CBT; adolescents with both medication and behavioural therapy (BT) and adults with pharmacotherapy. Stimulants are more efficacious than non-stimulants. Therapy starts with a methylphenidate agent unless there is an underlying anxiety disorder, risk for substance abuse or proven methylphenidate resistance. In these cases, treatment with atomoxetine is preferred. Seasonal affective disorder (SAD) is treated with light therapy, Vitamin D supplementation and/or short-term antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or bupropion and/or CBT.

Clinical Efficacy:

Atomoxetine, a selective norepinephrine reuptake inhibitor (SNRI), is more efficacious than placebo in the treatment of ADHD in children. Evidence suggests that atomoxetine efficacy is equivalent to methylphenidate and lower than with lisdexamfetamine in various age populations.

Bupropion, a dopamine/norepinephrine-reuptake inhibitor, is effective in the treatment of acute and long-term smoking cessation. In the treatment of depression, bupropion XL was found comparable in efficacy and safety to both venlafaxine XR and trazodone. Overall, bupropion was as efficacious as selective serotonin reuptake inhibitors (SSRIs); however, SSRIs demonstrated superiority in the setting of anxious depression.

Lithium, an antimanic agent, is more efficacious in preventing relapse in bipolar disorder than placebo or antidepressants. Lithium is more efficacious than anticonvulsants in preventing recurrences of manic episodes; however, limited evidence did not find lithium superior to other agents in the setting of depressive episodes. In the treatment of depression, lithium effectively augments the response of tricyclic

and second-generation antidepressants. The rate of suicide in mood disorders is reduced when therapy includes lithium.

Mirtazapine, an alpha-2 antagonist, demonstrates efficacy in the treatment of depression equivalent to SSRIs and superior to trazodone. Time to remission is shorter with mirtazapine than comparator agents. Evidence suggests that mirtazapine may be efficacious for treatment-resistant depression, geriatric depression, depression associated with agitation and anxiety and for the treatment of antipsychotic-induced akathisia.

Trazodone, a serotonin reuptake inhibitor/antagonist, is effective in the treatment of depression when compared with placebo. Limited evidence supports similar antidepressant efficacy as imipramine, nefazodone, trazodone and fluoxetine. Trazodone demonstrated efficacy in the off-label indications of insomnia and pediatric headache.

Vilazodone is an SSRI and partial $5HT_{1A}$ receptor agonist. It is more efficacious than placebo in the treatment of depression and may offer a more rapid response to therapy versus other antidepressants. Additional comparative clinical trials are needed to determine the clinical utility of vilazodone.

Vortioxetine is an SSRI and a $5HT_{1A}$ receptor agonist as well as a $5HT_3$ receptor antagonist. It is more efficacious than placebo in the treatment of depression. Limited evidence suggests vortioxetine outcomes compare to other serotonin-norepinephrine reuptake inhibitors (SNRIs). Vortioxetine may have additional utility in the setting of generalized anxiety disorders.

Safety:

Black Box Warnings:

Bupropion, mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine and atomoxetine medications are labeled with a Black Box Warning. [1,2]: Use of these agents is associated with an increased risk of suicidal thoughts and behaviors in children, adolescents and young adults. Lithium labeling includes a Black Box Warning reminding prescribers that toxicity is related to serum levels, that that toxic levels occur at near therapeutic levels and toxic levels may not differ overlap and that the drug should be initiated only with the availability of lithium monitoring.[1,2]

Adverse Events / Serious Adverse Events:

The most common adverse events associated with atomoxetine at an incidence greater than 10% include increased, headache, insomnia, drowsiness, hyperhidrosis, xerostomia, nausea, decreased appetite, abdominal pain, vomiting, constipation, erectile dysfunction, tachycardia and systolic/diastolic blood pressure elevations. Serious adverse events associated with atomoxetine use include myocardial infarction, sudden cardiac death, liver injury or failure, cerebrovascular accident, dyskinesia, seizure, mania, psychotic disorder, priapism and angioedema.

The most common adverse events associated with bupropion occurring at an incidence greater than 10% are tachycardia, headache, agitation, dizziness, insomnia, diaphoresis, weight loss, xerostomia, nausea, constipation, blurred vision and pharyngitis. Serious adverse events associated with bupropion use include complete atrioventricular block, myocardial infarction, colitis, pancreatitis, pancytopenia, abnormal liver function, hepatitis, jaundice, liver damage, anaphylactoid reaction, anaphylaxis, delayed hypersensitivity disorder, rhabdomyelosis, seizure, delusional disorder, worsening depression, hallucinations, hostile behavior, activation of hypomania.

The most common adverse events associated with lithium use at an incidence greater than 10% include acne, hypothyroidism, weight gain, gastritis, nausea, xerostomia, leukocytosis, fine tremor, deep

tendon hyperreflexia, nephrotoxicity, polyuria, and increased thirst. Serious adverse events associated with lithium use include bradyarrhythmias, Brugada syndrome, sinus node dysfunction, reduction in peripheral circulation (transient), erythema multiforme, ataxia, coma, pseudotumor cerebri, increased intracranial pressure, papilledema, epileptiform seizure, blurred vision, tinnitus, giddiness, renal interstitial fibrosis and angioedema.

The most common adverse events associated with mirtazapine use at an incidence greater than 10% include increased appetite, elevated triglycerides/cholesterol, weight gain, xerostomia constipation, and somnolence. Serious adverse events associated with mirtazapine use include agranulocytosis, neutropenia, liver cirrhosis, grand mal seizure, status epilepticus, exacerbation of depression, neuroleptic malignant syndrome and serotonin syndrome.

The most common adverse events associated with nefazodone use at an incidence greater than 10% include orthostatic hypotension, constipation, nausea, xerostomia, asthenia, confusion, dizziness, headache, lightheadedness, agitation, drowsiness, insomnia, somnolence, weakness and blurred vision. Serious adverse events associated with nefazodone use include neutropenia, electrocardiogram changes, Stevens-Johnson syndrome, hepatitis/liver failure, anaphylaxis, seizures (rarely), serotonin syndrome, exacerbation of depression, priapism and angioedema.[2,3]

The most common adverse events associated with trazodone use at an incidence greater than 10% include nausea, xerostomia, dizziness, headache, somnolence, blurred vision, nervousness and fatigue. Serious adverse events associated with trazodone use include cardiac dysrhythmia, hypotension, prolonged QT interval, torsades de pointes, hypersensitivity reactions, seizure, serotonin syndrome and priapism.

The most common adverse events associated with vilazodone use at an incidence greater than 10% include diarrhea, nausea, vomiting, and headache. Serious adverse events associated with vilazodone use include premature ventricular beats, abnormal bleeding, withdrawal syndrome and serotonin syndrome.

The most common adverse event associated with vortioxetine use at an incidence greater than 10% is nausea. Although self-reporting of sexual dysfunction was low, scores on the Arizona Sexual Experience Scale did exceed 10% for both men and women. Serious adverse events associated with vortioxetine use include hyponatremia, abnormal bleeding, activation of mania/hypomania and serotonin syndrome.

Summary:

Overall, each of the miscellaneous serotonergic agents demonstrates efficacy in the treatment of labeled indications. Evidence supports the use of bupropion in the treatment of smoking cessation. Evidence supports the use of atomoxetine in the treatment of ADHD with efficacy similarly to methylphenidate. Evidence supports the use of lithium in bipolar disorder. Comparative trials among the miscellaneous serotonergic agents in the treatment of depression are limited and evidence is insufficient to identify any agent(s) with superior efficacy. The miscellaneous serotonergic medications differ in their adverse event profiles. Limited comparative evidence finds the agents safe. Individualization of therapy is recommended with consideration of the patient age, history, comorbidities, type and severity of mental disorder, underlying disease and concurrent medications.

Introduction

The first antidepressant was discovered in the 1950s while researching treatments for schizophrenia.[4,5] Imipramine altered the brain's neurotransmitters and resulted in feelings of euphoria. Many other antidepressant medications with a similar three-ring chemical structure became available over the next couple of decades. Unfortunately, these "tricyclic" antidepressant (TCA) agents also resulted in serious adverse effects including somnolence, anticholinergic effects and overdose deaths.[6] In the 1980s, the development of a more targeted class of antidepressant medications, known as selective serotonin reuptake inhibitors (SSRIs), provided safer options for patients with mental health disorders. The SSRIs demonstrated similar rates of efficacy as the TCAs but with reduced rates of adverse effects and lower risk of death from overdose. By 1990, fluoxetine (Prozac®), an SSRI antidepressant, was listed as one of the most highly prescribed agents in the US, with ~65,000 prescriptions filled monthly and over $1 billion in annual sales.[4] The development of new antidepressant agents with varying neurotransmitter selectivity and unique mechanisms of action continues today with the goal of creating highly effective and safe therapeutic treatment options.

As a class, the antidepressant agents are indicated in the treatment of a variety of mental health disorders (including depression, anxiety and other mood disorders) as well as some non-psychiatric conditions (including musculoskeletal pain, neuropathies, fibromyalgia, insomnia and tobacco abuse).[7-10] The antidepressants may be categorized into different subclasses depending on mechanism of action and serotonergic activity including TCAs, monoamine oxidase inhibitors (MAOIs), SSRIs, selective serotonin-and-norepinephrine-reuptake inhibitors (SNRIs), serotonin modulators and many other miscellaneous agents. The agents that make up these serotonergic subclasses are associated with several Food and Drug Administration (FDA) approved indications, varying mechanisms of action and differing rates of adverse events/drug interactions.[7,8] This report will focus on the miscellaneous and serotoninergic agents: atomoxetine, bupropion, lithium, mirtazapine, nefazodone, trazodone, vilazodone and vortioxetine. All of the miscellaneous agents are available in oral tablet or capsule formulations and are labeled for use in the treatment of mental health disorders.[9,10] See Table 1 for a summary of the included agents and Table 2 for a review of the labeled indications for each of the agents.

Table 1. Comparison of the Miscellaneous and Serotonergic Agents[9,10]

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Antidepressants						
Bupropion (Wellbutrin®; Wellbutrin® SR; Wellbutrin® XL; Zyban®)	Oral tablet, as hydrochloride: 75 mg, 100 mg Oral tablet, 12-hour extended release (SR), as hydrochloride: 100 mg, 150 mg, 200 mg Oral tablet, 24 hour extended release, as hydrobromide (Aplenzin®): 174 mg, 348 mg, 522 mg Oral tablet, 24 hour extended release (XL), as hydrochloride: 150 mg, 300 mg, 450 mg	**Major depressive disorder** (Aplenzin, Forfivo XL, Wellbutrin, Wellbutrin SR, Wellbutrin XL) **Seasonal affective disorder** (Aplenzin, Wellbutrin XL) **Smoking cessation** (Buproban and Zyban)	Attention deficit hyperactivity disorder; Depression associated with bipolar disorder; Promotion of weight loss	Depression IR: 100 mg 2-3 times daily; max dose 450 mg daily in 3 or 4 divided doses SR: 150 mg twice daily; max dose 200 mg twice daily XL, HCL: 150-300 mg once daily; max dose 300 mg/day, guidelines state up to 450 mg/day XL, Hydrobromide: 174-348 mg once daily; max dose 522 mg daily *Switching from HCL (bupropion IR, SR, XL) to hydrobromide (Aplenzin): Bupropion HCL 150 mg daily = bupropion hydrobromide 174 mg daily Bupropion HCL 300 mg daily = bupropion hydrobromide 348 mg daily Bupropion HCL 450 mg daily = bupropion hydrobromide 522 mg daily Seasonal affective disorder; initiate treatment in autumn prior to symptom onset & discontinue in early spring with dose tapering XL, HCL: 150-300 mg once daily XL, Hydrobromide: 174-348 mg once daily Smoking cessation (Zyban, Buproban; begin at least 1 week before target quit date) 150 mg twice daily for 7-12 weeks; max dose 300 mg daily	Not indicated	Yes

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Mirtazapine (Remeron®; Remeron® SolTab™)	Oral tablet: 7.5 mg, 15 mg, 30 mg, 45 mg Oral tablet, dispersible: 15 mg, 30 mg, 45 mg	**Major depressive disorder**	Obsessive-Compulsive Disorder, Post Traumatic Stress Disorder	15-45 mg daily	Not indicated	Yes
Serotonin Modulators						
Nefazodone (Serzone®)	Oral tablet: 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	**Depression**	None listed	150-600 mg daily in 2 divided doses	Not indicated	Yes
Trazodone (Desyrel®)	Oral tablet: 50 mg, 100 mg, 150 mg, 300 mg Oral tablet, Extended Release (Oleptro®); 150 mg, 300 mg	**Treatment of major depressive disorder**	Antidepressant augmentation, Insomnia	IR: 150 mg daily in divided doses; maximum dose 600 mg daily (inpatients), 400 mg daily (outpatients)	Not indicated	Yes
Vilazodone (Viibryd®)	Oral tablet: 10 mg, 20 mg, 40 mg; starter pack (10 & 20 mg)	**Major depressive disorder**	None listed	20-40 mg once daily *Dosing adjustment recommended with concomitant strong CYP3A4 inhibitors/inducers	Not indicated	No
Vortioxetine (Trintellix ®)	Oral tablet: 5 mg, 10 mg, 20 mg	**Major depressive disorder**	None listed	5-20 mg once daily **Dosing adjustment recommended with concomitant strong CYP2D6 inhibitors/inducers and poor metabolizers	Not indicated	No
Central Nervous System Agents						
Atomoxetine (Strattera®)	Oral capsule: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg	**Attention-deficit/hyperactivity disorder**	Binge eating disorder, Nocturnal enuresis	40-100 mg once daily **Dosing adjustment recommended with concomitant strong CYP2D6 inhibitors/inducers and poor metabolizers	Children ≥6 years and ≤70 kg: 0.5 mg/kg/day, increase after minimum of 3 days to ~1.2 mg/kg/day; max 1.4 mg/kg or 100 mg, whichever is less	No

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Antimanic Agents						
Lithium (Eskalith CR®; Eskalith®; Lithobid® Slow-release)	Oral capsule: 150 mg, 300 mg, 600 mg Oral solution: 8 mEq/5 mL Oral tablet: 300 mg Oral tablet, Extended Release: 300 mg, 450 mg	**Bipolar disorder**	Bipolar depression, Augmentation of antidepressant	IR: 900-1,800 mg daily in 3 to 4 divided doses ER: 900-1,800 mg daily in 2 divided doses *Monitor serum concentrations and clinical response (efficacy and toxicity) to determine proper dose	Children 6 to 12 years: off-label Children >12 years and Adolescents: Refer to adult dosing	Yes

Key: IR = immediate release; ER: extended release; SR: 12-hour extended release; XL: 24-hour extended release; DCS - ; CYP – Cytochrome P450 (enzyme)

Table 2. Miscellaneous Serotonergic Agents FDA-Labeled Indications[9,10]

	Major Depressive Disorder	Bipolar Disorder	Attention-deficit/hyperactivity disorder	Seasonal Affective Disorder	Smoking Cessation
Antidepressants					
Bupropion (Wellbutrin®; Wellbutrin® SR; Wellbutrin® XL; Zyban®)	X			X	X
Mirtazapine (Remeron®; Remeron® SolTab™)	X				
Serotonin Modulators					
Nefazodone (Serzone®)	X				
Trazodone (Desyrel®)	X				
Vilazodone (Viibryd®)	X				
Vortioxetine (Trintellix®)	X				
Central Nervous System Agents					
Atomoxetine (Strattera®)			X		
Antimanic Agents					
Lithium (Eskalith CR®; Eskalith®; Lithobid® Slow-release)		X			

Disease Overview

Mental illness is defined as any diagnosable mental disorder with sustained abnormalities in behavior, mood or thinking that result in impaired functioning and distress.[11] Diagnosable mental disorders may include anxiety disorders, mood disorders, personality disorders, attention deficit disorders, schizophrenia, addiction disorders and feeding/eating disorders.[12] The most commonly reported mental illnesses in adults in the United States (US) are anxiety and mood disorders, including depression and bipolar disorder.[11] The most commonly reported mental illnesses in adolescents in the US are depression and attention deficit disorders.[13] All mental illnesses can cause severe disruptions in activities of daily living and result in premature death. According to the World Health Organization (WHO), mental health disorders cause more patient disability than cancer, heart disease or any other illness.[11] In addition, mental health disorders are associated with increased rates of comorbid chronic diseases (including cardiovascular disease, diabetes, obesity, asthma, epilepsy and cancer); inappropriate use of medical care (including treatment nonadherence and increased emergency department visits); use of tobacco products, abuse of alcohol and other substances; increased rates of intentional and unintentional injuries and an overall increase in adverse health outcomes.[11] According to the Centers for Disease Prevention and Control (CDC), approximately 25% of all adults currently have a mental illness and up to 50% of adults will report a mental illness during their lifetime resulting in an economic burden of nearly $300 billion in the US (2002).[11] Increased access to mental health treatment services results in successful management of the mental health disorder, reduced rates of mortality and morbidity and improved health outcomes for comorbid chronic diseases.[11]

Major Depressive Disorder

The mood disorders (including depressive disorder, bipolar disorder, etc.) affect approximately one in ten adult Americans.[14] Major depressive disorder is the most common of the mood disorders, affecting nearly 15% of US adults.[15] In 2004, depression was listed as the third most common cause of disease burden across the world.[16] In general, depression occurs more frequently in women than men, in the 40-59 year age range, and in patients living below the poverty level. Depressive disorder is linked to increased rates of chronic disease, health care utilization and impaired activities of daily living. Almost half of all patients with depression experience inabilities to maintain healthy work, home and social habits. The economic burden of depression in the US (~$83.1 billion in 2000) results from the combined costs associated with increased rates of indirect costs (unemployment, lost productivity, etc.) in addition to direct healthcare costs.[13,17] Depression is frequently underdiagnosed and, even more frequently, depression is inadequately treated. Improving disease education and increasing access to care will help to improve clinical outcomes and save costs.[12]

Depression is a serious mental disorder characterized by changes in cognitive and physical behaviors with a loss of pleasure in enjoyable activities.[12] Major depression is defined as the presence of at least 5 symptoms during a minimum of a 2-week period that reflect a change in previous functioning and cause distress or impairment in normal activities. Symptoms associated with a depression episode must include sadness and/or loss of interest or pleasure and may also include significant unexplained weight loss, insomnia or hypersomnia, agitation, fatigue, feeling worthless or excessive guilt, reduced ability to concentrate and recurrent thoughts of death. In some patients (< 2% of the general population), depression may not be clearly associated with

acute distress, impairment or change from previous functioning. Dysthymic disorder is defined as a persistent depressive mood with chronic (≥2 years) with ongoing symptoms that tend to be less severe and/or numerous than for diagnosis of major depressive disorder.[12]

Drug therapy is the foundation of the medical management of the mood disorders. Before the introduction of the second-generation antidepressants, drug therapy was limited to TCAs and MAOIs, known collectively as the first-generation antidepressants. The first generation antidepressants are associated with many intolerable adverse effects (sedation and anticholinergic effects) and are no longer agents of choice for treating depressive disorders. As a result, the second-generation antidepressants, including the selective serotonergic agents and serotonin modulators, are one of the leading drug classes in the US pharmaceutical market and accounted for $10.9 billion in US prescription sales in 2003.[13,17] Clinical evidence suggests the most efficacious treatment for depression includes a combination of psychological therapy and medication therapy for at least 6-8 weeks with a treatment plan to reduce the risk of disease/symptom recurrence.[13] Almost half of all patients being treated for depression by their primary care provider will discontinue their medication therapy within a month, unless proper education and a treatment plan are provided. Selection of an antidepressant agent should be based on treatment history, comorbid conditions and patient preference. In patients demonstrating suicidal ideation, for example, drug selection should be based on agents with low toxicity if taken in overdose.[12]

Clinical guidelines for the treatment of depression include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders (2013),[18] the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010)[19], the National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)[20] and American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007).[21] See Table 3 for a summary of the most current guideline recommendations. In general, the guidelines recommend use of a second-generation antidepressant for the treatment of depression. First-line agents typically include those for which the patient has had a previous positive response or a family history of a positive response. If only a partial response is achieved at 6-8 weeks, referral to a mental health specialist is recommended. Partial responders should receive an alternative antidepressant, a combination of antidepressant agents or adjunctive treatment with another class of medications including lithium, thyroid hormone, atypical antipsychotic agent or dopamine agonist. A large randomized controlled trial examining Sequenced Treatment Alternatives to Relieve Depression (STAR*D) did not report any differences in efficacy between the adjunctive medication classes.[22] Medication therapy should be adjusted until full remission is achieved and treatment should be continued for an additional 6-9 months to prevent relapse. Chronic maintenance therapy is recommended in patients with two or more depression episodes. Cognitive Behavioral Therapy (CBT) is recommended for all patients with depressive disorder.[12]

Table 3. Current Clinical Practice Guidelines for the Treatment of Depressive Disorders

Guideline	Recommendations

World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorder (2013)[19]	• Medication therapy in combination with psychological counseling is recommended
	• A treatment plan and disease/medication education are recommended for all patients
	• Antidepressant agents are recommended as first-line
	  ○ No single class of antidepressants has proven to be more effective than another
	  ▪ Amitriptyline, clomipramine and venlafaxine have demonstrated increased efficacy in severely depressed hospitalized patients
	• Second- (bupropion, trazodone) and third- (SSRI, SNRIs, mirtazapine) generation antidepressants are generally better tolerated than the older agents
	• In treatment-resistant patients: increasing the dose, switch to another antidepressant agent, combine two antidepressants, augmenting the antidepressant with other agents (best evidence for aripiprazole, lithium, quetiapine)

National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)[20]	<u>Mild-Moderate Disorder</u> First-line: low-intensity psychosocial intervention Second-line: antidepressant therapy (typically SSRI) OR a high-intensity psychosocial intervention <u>Moderate-Severe Disorder</u> First-line: combination antidepressant therapy and a high-intensity psychological intervention <u>Antidepressant agents</u> • SSRIs have a favorable risk-benefit ratio • Fluoxetine, fluvoxamine and paroxetine are associated with increased risk of drug interactions • Venlafaxine and tricyclic antidepressants are associated with increased risk of death from overdose • MAOIs should only be prescribed by specialists • In treatment-resistant patients, increase dose or switch to another antidepressant

American Psychiatric Association (APA): Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010) [21]	<u>Acute phase</u>
	First-line: antidepressant medication (SSRI, SNRI, bupropion, mirtazapine)
	• The effectiveness of antidepressant medications are comparable and initial selection is based on adverse effect profile, prior treatments, cost and patient preference
	  ○ If side effects occur, lower dose or switch agents
	  ○ If no response or partial response: increase dose, switch agents or augment the antidepressant with another antidepressant or a non-antidepressant medication (lithium, thyroid hormone or a second generation antipsychotic)
	
	<u>Continuation phase</u>
	Continue successful treatment for 6-9 months and monitor for signs of relapse

Guideline	Recommendations
	Maintenance phase Continue successful treatment in patients with three or more depressive episodes or with additional risk factors for relapse Discontinuation of treatment Taper the medication over the course of at least several weeks Other notes Combination of antipsychotic and antidepressant medications is recommended in patients with psychotic symptoms
Institute for Clinical Systems Improvement (ICSI): Major Depression in Adults in Primary Care (2011)[23]	Recommended pharmacotherapy: SSRIs, venlafaxine, duloxetine, desvenlafaxine, mirtazapine, bupropion Other options: Secondary amine TCAs, MAOIs Augmentation therapy: bupropion, buspirone, mirtazapine, triiodothyronine (T3), stimulants, TCA-SSRI combination, lithium, atypical antipsychotics **Recommended in patients with treatment-resistant or partially-responsive disease and referral to a mental health specialist is advised
Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults (2009)[24]	Selection of an antidepressant agent should be based on disease severity, comorbid conditions, adverse effect profile, treatment history, potential drug–drug interactions, patient preference and cost; Use of antidepressant should be accompanied by patient education, close monitoring (1-4 weeks) and self-management techniques First-line recommendations Bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, sertraline, venlafaxine Second-line recommendations Amitriptyline, clomipramine and other TCAs; quetiapine; selegiline; trazodone Third-line recommendations Phenelzine, tranylcypromine
American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007)[21]	• A confidential relationship should be maintained with the child or adolescent • Psychiatric assessments should routinely be made • Treatment should always include an acute and continuation phase, some may require maintenance treatment First-line: supportive psychotherapy Second-line: psychotherapy and/or antidepressants o SSRIs are the most commonly used pharmacotherapy in pediatric patients o Clinical response should be assessed at 4-week intervals

Guideline	Recommendations
	▪ If inadequate response, increase dose ○ Treatment should be continued for 6-12 months ○ Atypical antipsychotics, combined with SSRIs, are recommended as the treatment of choice for depressed psychotic pediatric patients

Key: SSRI – selective serotonin reuptake inhibitor; SNRI – serotonin norepinephrine reuptake inhibitor; MAOI – monoamine oxidase inhibitor; TCA – tricyclic antidepressant.

Bipolar Disorder

Bipolar disorder (or manic-depressive disorder) is a mood disorder characterized by episodes of depression and mania.[25] The prevalence of bipolar disorder is 0.4-1.4% across the world and 4% in the US.[16,26] In general, bipolar disorder occurs more frequently in women than men and the average age of first onset of the disease is 25 years. Bipolar disorder is the most expensive mental health disorder, with costs reportedly double those of depression per affected individual. The economic burden of bipolar disorder in the US results from indirect costs due to lost productivity resulting from absenteeism and presenteeism in addition to direct healthcare costs.[16] Bipolar disorder is also associated with an increased rate of substance abuse, legal and financial complications, relationship difficulties, self-harm and serious suicide attempts. Successful disease management and early treatment intervention can help to improve health outcomes and reduce the economic burden of bipolar disorders.[16]

The depression-mania cycles associated with bipolar disorder are unpredictable with mania episodes typically emerging over a period of days to weeks and persisting up to several weeks or months. Mania is defined as clearly elevated moods with unrestrained behaviors lasting at least a week with at least 3 symptoms, which may include irritability, grandiosity, sleeplessness, pressure talking, distractibility or engaging in activities with a high potential for adverse consequences. Clinical evidence suggests anger and agitation are the most common symptoms in pediatric patients while disordered thought content occurs most frequently in adult patients.[27] In severe mania, symptoms similar to those seen in schizophrenia, including delusions and paranoid thinking, may present. The depression episodes are defined as a persistent low mood including lack of positive affect and anhedonia causing impairment for greater than 2 weeks. In bipolar II disorder patients may lack the full criteria for mania and the recurrent depression episodes are instead separated by hypomania episodes with mild activation and increased energy.[28]

Treatment of bipolar disorder includes psychotherapy and medication therapy (mood stabilizers and antidepressant medications). Mood stabilizers may include lithium, anticonvulsant therapies and antipsychotic agents. Lithium is typically the first-line agent and has demonstrated efficacy in the treatment of bipolar disorder with a response rate of 70-80%, beneficial effects within 1-2 weeks and prophylactic effects. Antidepressants are effective in treating breakthrough depression episodes but may precipitate mania or accelerate cycle frequency. Recent clinical evidence suggests mood stabilizers demonstrating efficacy for mania are also efficacious for mixed episodes, reducing the need for antidepressant therapy.[29] Antipsychotic agents (such as aripiprazole, asenapine, cariprazine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone) may be used alone or in combination with other mood stabilizers or antidepressants to maintain

mood stability, control agitation or treat bipolar disorder in patients experiencing loss of efficacy with lithium therapy.[12,CDC, 2016 #2670]

Clinical guidelines for the treatment of bipolar disorder include the WFSBP: Guidelines for Biological Treatment of Bipolar Disorder (2013)[30-32], the American Psychiatric Association Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)[33], NICE guideline for Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014)[34] and AACAP: Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007).[35] See Table 4 for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment for acute mania episodes and acute depression episodes and maintenance therapy in patients at high risk for recurrence or severe disease. For selection of pharmacotherapy in the treatment of acute mania or depression episodes, factors to consider include symptoms such as euphoric, mixed, psychotic, suicidality; severity; treatment history; adverse effect profile and patient preference.[30-32]

Medication therapy for acute mania episodes (lithium, valproate, aripiprazole, risperidone, ziprasidone, etc.) should be continued until full remission.[30-32,34,35] If no response or only a partial response is achieved after 2 weeks of therapy, increase the dose of the medication or switch to another agent. Combination therapy is recommended in patients with continued treatment-resistance to a single agent. In patients with severe mania, clozapine or electroconvulsive therapy (ECT) may be indicated. Recommendations for antidepressant therapy in the treatment of acute depression episodes are inconsistent. In general, medication therapy for acute depression episodes (first- or second-generation antidepressants, lithium, quetiapine, olanzapine, lamotrigine, etc.) should be provided in an established treatment setting, in combination with behavioral therapy and regularly assessed for both efficacy and adverse effects. Before initiation of treatment for acute depression, all other potential medical causes should be ruled out and caffeine, alcohol and other substances should be discontinued. Of note, the full therapeutic effects of antidepressant therapy, lithium and lamotrigine may take several weeks; additional symptomatic treatment with benzodiazepines during the first few weeks of an acute bipolar episode may be required. Maintenance therapy is recommended in patients with three or more acute episodes, two acute episodes and a positive family history for bipolar disorder or in patients with severe disease.[30-32,34,35]

Table 4. Current Clinical Practice Guidelines for the Treatment of Bipolar Disorder

Guideline	Recommendations
World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorder (2013)[30-32]	Treatment of an acute mania episode, any one of the following: • aripiprazole 15-30 mg daily • lithium 600-1200 mg daily (serum level 0.8-1.3 mmol, only if chronic treatment is being considered) • risperidone 2-6 mg daily • valproate 1200-3000 mg daily (loading dose 20-30 mg/kg; serum level 75-100 mg; not preferred in women of childbearing age) • ziprasidone 80-160 mg daily Treatment of acute depressive episode: • best evidence: quetiapine 300-600 mg daily

Guideline	Recommendations
	• good evidence: fluoxetine/olanzapine combination therapy • fair evidence: bupropion, fluoxetine, imipramine, sertraline, tranylcypromine, venlafaxine in combination with a antimanic agent; lithium monotherapy; lithium in combination with lamotrigine Maintenance treatment, best evidence for: • aripiprazole • lamotrigine • lithium • quetiapine
National Institute for Health and Clinical Excellence (NICE) Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014)[34]	<u>Adults</u> Mania • haloperidol, olanzapine, quetiapine or risperidone • lithium alone or in combination with haloperidol, olanzapine, quetiapine or risperidone Depression • fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine • lithium alone or in combination with fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine Maintenance Therapy • lithium alone or in combination valproate • valproate, olanzapine, quetiapine <u>Precautions</u> • There is an increased risk for side effects in young patients ○ Antipsychotic treatment is not recommended for longer than 12 weeks in young patients • For treatment of depression in young patients, a structured psychological intervention for at least 3 months is recommended • Lithium and/or valproate should not be initiated in primary care • Do not use lamotrigine for acute mania or mixed episode
American Psychiatric Association (APA): Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)**[33] ****"This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice"**	Acute manic or mixed episodes • Adjunctive antipsychotic therapy should be considered in manic or mixed manic episodes with psychotic features ○ Second-generation agents are recommended over first-generation agents due to side effect profile Acute depressive episodes • Adjunctive antipsychotic therapy or electroconvulsive therapy is recommended in acute depressive episodes with psychotic features Maintenance • Adjunctive antipsychotic therapy should be closely monitored, reassessed and slowly tapered, if indicated Acute rapid cycling • Combination therapy with a second-generation antipsychotic may be indicated

Guideline	Recommendations
Veterans Affairs/Department of Defense (VA/DoD): Clinical Practice Guideline for Management of Bipolar Disorder in Adults (2010)[36]	Mania: Agents most likely to be beneficial include lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone; lithium or valproate may be combined with an atypical antipsychotic Mixed episode: Agents most likely to be beneficial include valproate, carbamazepine, aripiprazole, olanzapine, risperidone or ziprasidone Depression: Agents most likely to be beneficial include quetiapine, lamotrigine, lithium, olanzapine/fluoxetine, olanzapine Notes: **Treatment response should be evaluated at 4 to 8 weeks and periodically until full remission **Patients who have failed monotherapy for mania: consider switching to another monotherapy or combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotic **Treatment of severe mania or mixed episode: clozapine with valproate or lithium ** Treatment of severe depression: clozapine
The Texas Medication Algorithm Project (TMAP): Texas Implementation of Medication Algorithms (TIMA) Procedural Manual: Bipolar Disorder Algorithms (2007)[4]	Hypomania or mania <u>Stage 1</u> Euphoric symptoms: lithium, valproate, aripiprazole, quetiapine, risperidone, ziprasidone Mixed symptoms: valproate, aripiprazole, risperidone, ziprasidone <u>Stage 1b</u> olanzapine and carbamazepine are alternatives <u>Stage 2</u> combination therapy with two: lithium, valproate, olanzapine, quetiapine, risperidone, or ziprasidone (not 2 antipsychotics) <u>Stage 3</u> a different combination than in Stage 2, with additional options: carbamazepine, oxcarbazepine, aripiprazole, a first-generation antipsychotic <u>Stage 4</u> clozapine or a 3-drug combination including lithium, an anticonvulsant mood stabilizer (valproate, carbamazepine, or oxcarbazepine) an atypical antipsychotic agent Depression <u>Stage 1</u> lamotrigine monotherapy for patients without a recent and/or severe history of mania OR lamotrigine plus a mood stabilizer <u>Stage 2</u> quetiapine monotherapy or olanzapine/fluoxetine combination treatment <u>Stage 3</u> evidence-based medicine is limited

Guideline	Recommendations
American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007)[35]	Standard therapy (based on adult literature): lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated; antidepressants may be used as adjunctive therapy for bipolar depression The choice of medication should be based on • evidence of efficacy • illness phase • presence of confounding symptoms • side effects • patient's medication response history • patient and family preferences Additional notes • clozapine or electroconvulsive therapy are reserved for treatment-refractory cases • maintenance medication therapy may be recommended to prevent relapse • baseline and follow-up review of symptoms/efficacy, adverse effects and laboratory monitoring is recommended • 6-8 week trial of a mood-stabilizing agent is recommended before switching agents or adding an additional agent • psychotherapy is recommended as part of a comprehensive treatment plan

Attention Deficit Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by inattention, hyperactivity and impulsivity. ADHD is most often a disorder of childhood that may continue into adulthood. According to a National Survey of Children's Health (2010-2012), over 10% (~6.4 million) of US school-aged children have a diagnosis for ADHD and this number continues to rise with an increase of 42% reported between 2003 and 2011. In general, ADHD is diagnosed more frequently in school-aged boys (1 in 5) than in school-aged girls (1 in 11) and the average age of first onset of the disease is 7 years. The prevalence of ADHD in US adults is estimated to be 4.1%. The economic burden of ADHD in the US (reaching $52 billion in 2005) results from the combined costs associated with the treatment of patients and lost productivity for patients and family members.[37-39] In addition, ADHD frequently occurs in combination with other mental health disorders (up to ~50%) including aggression-related disorders (Oppositional Defiant Disorder or Conduct Disorder), learning ability disorders, depression and anxiety, which may further contribute to increased costs and morbidity. Increasing mental health disorder education and screening can help to improve patient outcomes and reduce overall costs.[40]

ADHD is defined as a mental disorder with inattention (difficulty sustaining focus and disorganized not due to incomprehension), hyperactivity (restlessness and excessive movement/talking) and/or impulsivity (hasty actions with high potential for harm and/or inability to delay gratification) that result in difficulty functioning at school and at home. ADHD may be divided into three different types: predominantly inattentive, predominantly hyperactive-impulsive

or combined presentation with symptoms of both types equally exhibited.[41] There is no single test to diagnose ADHD. In general, diagnosis requires symptoms persisting at least 6 months including 6 or more symptoms of inattention and/or hyperactivity-impulsivity for children <16 or 5 or more symptoms for adolescents and adults >17. Symptoms of inattention may include failure to pay close attention to details, making careless mistakes, trouble maintaining attention on a single task, inability to listen, failure to finish duties, trouble organizing tasks, avoids tasks that require mental effort over a long period of time, frequently losing things, and easily becoming distracted or forgetful. Symptoms of hyperactivity-impulsivity may include fidgeting, trouble remaining seated, feeling restless (may run or climb), trouble participating in quiet activities, "on the go," talking excessively, speaking out of turn, trouble waiting for turn, and often interrupting or intruding. For diagnosis, symptoms should be present before age 12, present in two or more settings and should reduce the quality of school/work and social functioning.[42]

Treatment of ADHD should include a combination of behavior therapy and medication therapy. For preschool-aged children, behavior therapy alone is recommended as first line.[41] Behavioral therapies include teaching the child new behaviors to replace ones that cause disruptions to activities of daily living in addition to instructing the child's parents to teach and enforce skills to help the child manage their behavior. Medication therapy may include stimulant and nonstimulant agents. Stimulants, including amphetamine and methylphenidate agents, are the most widely used ADHD treatments, are fast-acting and are efficacious in reducing ADHD symptoms. Nonstimulant agents, including atomoxetine (Strattera®), guanfacine, and clonidine are not as fast-acting but are long-acting and may be associated with fewer adverse effects. Often it requires multiple trials of different medications at various doses to find the optimal drug therapy in children with ADHD.[43] Effective treatment plans should include both behavioral and medication therapy, close monitoring and frequent follow-ups.[33,41,44,45]

Clinical guidelines for the treatment of attention-deficit/hyperactivity disorder include the American Academy of Child and Adolescent Psychiatry guidelines on Attention-Deficit/Hyperactivity Disorder (2007)[46], the American Academy of Pediatrics guidelines on Attention-Deficit/Hyperactivity Disorder (2011)[47] and the National Collaborating Centre for Mental Health NICE guidelines on Attention Deficit Hyperactivity Disorder (2008).[48] See Table 5 for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment with medication and behavioral therapy in children and adolescents with ADHD. In preschool-aged children, guidelines recommend behavioral therapy alone as first-line treatment of ADHD. In adults, guidelines recommend medication therapy alone as first-line treatment of ADHD. In general, evidence suggests stimulants are more efficacious than non-stimulants in the treatment of ADHD. Choice of medication therapy usually includes a methylphenidate agent as first-line, atomoxetine in patients with underlying anxiety disorder or risk for substance abuse and an amphetamine agent in patients with methylphenidate-resistant disease. Some evidence suggests that clonazepam in addition to a stimulant agent may be helpful in children with only a partial response to stimulant monotherapy.[49] All patients should receive a well-thought-out treatment plan with close follow-up and appropriate titration of medication therapy.

Table 5: Current Clinical Treatment Practice Guidelines for Attention Deficit Disorder

Guideline	Recommendations
American Academy of Child and Adolescent Psychiatry guidelines on Attention-Deficit/Hyperactivity Disorder (2007)[46]	Initial medication therapy should be with a trial of an agent with a labeled indication for the treatment of ADHD by the FDA: dextroamphetamine, methylphenidate, mixed salts amphetamine or atomoxetine: • Stimulants are highly efficacious • Methylphenidate and amphetamine agents are equally efficacious in the treatment of ADHD • Long-acting formulations are equally efficacious as immediate-release agents but may be more convenient In patients with treatment-refractory disease, behavior therapy and/or the use of medications not approved by the FDA for the treatment of ADHD (bupropion or tricyclic antidepressants) should be considered All patient should be monitored for treatment-emergent side effects and assessed periodically for treatment efficacy • Patients treated with medication for ADHD should have height and weight monitored throughout treatment • Treatment of ADHD should continue as long as symptoms remain present and cause impairment
American Academy of Pediatrics guidelines on Attention-Deficit/Hyperactivity Disorder (2011)[47]	Recommendations vary depending on the patient's age: Preschool-aged children (4–5 years of age) • Evidence-based parent- and/or teacher-administered behavior therapy as the first line of treatment • Methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in functioning Elementary school–aged children (6–11 years of age) • FDA-approved medications for ADHD and/or evidence-based parent- and/or teacher-administered behavior therapy, preferably both ○ Evidence is strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine and extended-release clonidine (in descending order of strength of evidence) Adolescents (12-18 years of age) • FDA-approved medications for ADHD and/or evidence-based parent- and/or teacher-administered behavior therapy, preferably both • Medication therapy in all patient age groups should titrated to achieve maximum benefit with minimum adverse effects

National Collaborating Centre for Mental Health NICE guidelines on Attention Deficit Hyperactivity Disorder (2008)[48]	Treatment for children and young people
	• Parent-training/education programs are first-line for pre-school children; drug treatment is not recommended for pre-school children
	• Group-based parent-training/education programs are first-line for school-age children and young people with moderate impairment
	• Medication therapy is usually first-line for school-age children and young people with severe symptoms and impairment or for those with moderate impairment who have not responded to parent-training/education programs or group psychological treatment
	  ○ Drug treatment should only be initiated by an ADHD specialist
	  ○ Drug therapy includes: methylphenidate, atomoxetine and dexamphetamine
	  ▪ Methylphenidate for ADHD without significant comorbidity
	  ▪ Methylphenidate for ADHD with comorbid conduct disorder
	  ▪ Methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present

Guideline	Recommendations
	▪ Atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses ▪ Dexamphetamine in children and young people unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine ○ Extended-release preparations should be considered for convenience, improving adherence, reducing stigma, and in schools with rules against storing and administering controlled drugs ○ Immediate-release preparations should be considered for more flexible dosing regimens and during initial titration ○ Overall, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed Treatment for adults • Medication therapy is the first-line treatment for adults with moderate or severe levels of impairment ○ Methylphenidate is the first-line drug ○ Psychological interventions without medication may be effective for some adults with moderate impairment ○ Atomoxetine or dexamphetamine are recommended in patients who did not respond to methylphenidate treatment ○ There is potential for drug misuse and diversion in adults with ADHD receiving stimulants
Institute for Clinical Systems Improvement: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents (2012)[50]	Medication therapy • Use FDA-approved treatments for ADHD in children, including psychostimulants and/or non-stimulants • Decision to initiate medication therapy should be made in conjunction with parents and discussion of expected benefits and potential risks • Age, disease severity and presence of comorbidities should be considered • Optimal medication management alone is superior to other modalities for the core symptoms of ADHD • If patient does not respond to initial medication choice, a second or third trial with other stimulants is recommended • Atomoxetine is recommended in patients with comorbid anxiety, sleep initiation disorder, substance abuse or tics • Extended-release guanfacine and extended-release clonidine have a labeled indication as adjunctive therapy with stimulant medications • Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) a nontricyclic antidepressant (bupropion) or immediate-release guanfacine

Key: ADHD – attention deficit hyperactivity disorder; FDA – Food and Drug Administration

Seasonal Affective Disorder

Seasonal affective disorder (SAD) is a type of depressive disorder characterized by a serious mood shift that occurs during the fall and winter months.[51-53] Symptoms associated with the mood shift may include feelings of hopelessness or worthlessness, irritability, loss of interest in activities, fatigue, difficulty concentrating and/or thoughts of death or suicide. According to the National Institute of Mental Health, SAD affects over 10 million Americans. In general, SAD occurs more frequently in women than men and the average age of first onset of the disorder is 20 years. Seasonal affective disorder can affect quality of life and up to 6% of those diagnosed with SAD will require hospitalization. SAD is thought to be associated with the amount of daylight

available and the incidence increases in regions furthest away from the equator. Light therapy is considered first-line treatment for SAD; unfortunately, up to half of those diagnosed with SAD do not respond to light therapy. Recent clinical evidence suggests Vitamin D supplementation may be as effective as light therapy in the treatment of SAD but the available evidence is mixed. Short-term medication therapy with an antidepressant agent in combination with CBT may also be beneficial in the treatment of SAD. The SSRIs and bupropion are labeled for use in the treatment of seasonal affective disorder. Other suggested activities to reduce the symptoms of SAD include healthy sleep habits, nutritious meals, medication adherence, exercise and avoiding alcohol or illegal drugs. Patients should be counseled to watch for early signs of worsening depression and have a well-thought-out treatment plan in place for the recurrence and/or worsening of the disorder.[51-53]

Pharmacology

The exact mechanism of action of each of the serotonergic agents is not fully known. In general, the agents block the uptake and reuptake of serotonin and noradrenergic neurotransmitters, resulting in increased and prolonged serotonergic neurotransmission.[4,5] Initially, stimulation of autoreceptors on serotonergic terminals results in reduced serotonin synthesis and release, resulting in a "therapeutic lag" of the antidepressant effects. With repeated administration, a gradual down-regulation and desensitization of the serotonergic autoreceptors occurs and measurable therapeutic responses are detected after 3-4 weeks of medication therapy. In addition, studies demonstrate that long-term effects of antidepressant therapy result in additional adaptive and regulatory mechanisms that further enhance the effectiveness of antidepressant therapy. Similar to the "therapeutic lag" seen with initiation of antidepressant therapy, adverse effects reported with the agents occur more frequently and with greater severity during the first few weeks of therapy. After 2-4 weeks of ongoing therapy, adverse effects are reduced or disappear.[7,8]

Atomoxetine: The mechanism of action of atomoxetine is selective inhibition of the reuptake of norepinephrine. Atomoxetine does not appear to exhibit direct action on the release or reuptake of serotonin or any of the other neurotransmitters. Its peak efficacy develops over 2–6 weeks. It is initiated at a dose of 0.5 mg/kg/day and then increased to 1.2 mg/kg/day in 2 weeks.[33]

Bupropion: The mechanism of action of bupropion is related to weak inhibition of norepinephrine and dopamine uptake in the neuron.[6,7] Bupropion is an aminoketone antidepressant; it is structurally unique from other antidepressants and does not appear to inhibit the reuptake of serotonin. Active metabolites of bupropion further inhibit the reuptake of norepinephrine. Bupropion is eliminated through both hepatic and renal routes and patients with severe hepatic or renal disease should receive a dose of no more than 150 mg every other day[5]

Lithium: The exact mechanism of action of lithium in the treatment of mood disorders is not well understood but it is thought to be associated with alteration of cation transport in nerve and muscle cells, reuptake of serotonin and/or norepinephrine in neurons and inhibition of second messenger systems in the phosphatidylinositol cycle.[9,10] Pharmacological evidence also suggests lithium produces neuroprotective effects by “increasing glutamate clearance, inhibiting apoptotic glycogen synthase kinase activity, increasing the levels of antiapoptotic protein Bcl-2 and enhancing the expression of neurotropic factors, including brain-derived neurotrophic factor.”[54]

Lithium is a small monovalent cation similar to sodium in its properties. It was first used in the 19th century in the treatment of gout, briefly used as a sodium chloride substitute in patients with hypertension in the 1940's and found to be effective as a mood stabilizer in 1949 when it became the treatment of choice in bipolar disorder.[55] Serum lithium levels may be obtained starting 5 days after initiation of treatment and regularly repeated throughout therapy to assess therapeutic levels, optimize efficacy and reduce risk of adverse effects.

Mirtazapine: The mechanism of action of mirtazapine is thought to be associated with central presynaptic alpha-2 adrenergic antagonist effects resulting in increased release of serotonin and norepinephrine.[9,10] Mirtazapine does not appear to inhibit the reuptake of serotonin or norepinephrine, like other serotonergic antidepressants. It is a potent antagonist of serotonin receptors (specifically 5-HT2, 5-HT3), H1 histamine receptors and muscarinic receptors, which may play a part in the adverse effect profile of the drug. Mirtazapine elimination half-life is 16-30 hours, dose changes should not occur more often than every 1-2 weeks, and clearance is decreased in the elderly population and in patients with severe renal or hepatic disease.[8] Mirtazapine is also usually given in the evening due to its sedating effects.[56]

Nefazodone: The mechanism of action of nefazodone is the inhibition of serotonin and norepinephrine reuptake in the neuron.[9,10] Nefazodone is structurally similar to trazodone and appears to block 5-HT2 serotonin and alpha-1 receptors, which may be associated with postural hypotension. Nefazodone has a short half-life, is associated with rare but serious liver injury and is no longer commonly used by clinicians for the treatment of depression.[8,56]

Trazodone: The primary mechanism of action of trazodone is inhibition of the reuptake of serotonin.[9,10] Trazodone also causes adrenoreceptor subsensitivity, produces changes in presynaptic serotonin adrenoreceptors and significantly blocks H1 histamine and alpha-1 adrenergic receptors. Trazodone has a short half-life and undergoes extensive hepatic metabolism, limiting its bioavailability.[56] Trazodone is most commonly used in current practice as a hypnotic in patients with insomnia because it is highly sedating and does not produce tolerance or dependence like other hypnotic agents.[8]

Vilazodone: The mechanism of action of vilazodone is tied to inhibition of serotonin reuptake and partial agonism at serotonin 5-$_{HT1A}$ receptors with little to no effect on norepinephrine or dopamine neurotransmitters.[9,10] Of note, evidence suggests 5-HT_{1A} receptor activity may be altered in patients with depression and anxiety, which may affect vilazodone efficacy. Vilazodone is well absorbed (which is increased with a fatty meal) and is extensively metabolized by cytochrome P450 enzymes (primarily CYP3A4).[56]

Vortioxetine: The mechanism of action of vortioxetine is not well understood but appears to be tied to the selective reuptake of serotonin, agonistic activity at 5-HT1A receptors and antagonistic activity at 5-HT_3 receptors.[9,10] Vortioxetine does not appear to have any direct effect on norepinephrine or dopamine neurotransmitters. Vortioxetine is extensively metabolized by cytochrome P450 enzymes (primarily CYP2D6), is tightly protein-bound and exhibits dose-proportional pharmacokinetics.[56]

Table 6. Pharmacokinetic Properties of the Miscellaneous Serotonergic Agents[9,10,57]

Agent	Action	Distribution	Metabolism	Excretion	Half-life elimination
Antidepressants					
Bupropion	Absorption: Rapid Onset of action: 1 to 2 weeks Duration of action: 1 to 2 days Half-life: 3 to 4 hours	V_d: ~20 to 47 L/kg Protein binding: 84%	Extensively hepatic via CYP2B6 to hydroxybupropion; non-CYP-mediated metabolism to erythrohydrobupropion and threohydrobupropion. Metabolite activity ranges from 20% to 50% potency of bupropion. Bupropion also undergoes oxidation to form the glycine conjugate of meta-chlorobenzoic acid, the major urinary metabolite	Urine (87%, primarily as metabolites) Feces (10%, primarily as metabolites)	~21 hours after chronic dosing (range: 12 to 30 hours); Metabolites (after a single dose): Hydroxybupropion: 20 ± 5 hours; Erythrohydrobupropion: 33 ± 10 hours; Threohydrobupropion: 37 ± 13 hours ER (Aplenzin): 21 ± SD 7 hours; Metabolites: Hydroxybupropion: 24 ± 5 hours; Erythrohydrobupropion: 31 ± 8 hours; Threohydrobupropion: 51 ± 9 hours
Mirtazapine	Absorption: Rapid and complete Bioavailability: ~50% Time to peak, serum: ~2 hours	Vd: unknown Protein binding: ~85%	Extensively hepatic via CYP1A2, 2D6, 3A4 and via demethylation and hydroxylation	Urine (75%) and feces (15%) as metabolites	20 to 40 hours; increased with renal or hepatic impairment
Serotonin Modulators					
Nefazodone	Absorption: Rapid; well absorbed; food delays absorption by ~20% Bioavailability: 20% (variable); food decreases bioavailability by ~20%; AUC increased by 25% in patients with cirrhosis of the liver Time to peak, serum: Children and Adolescents: 0.5 to 1 hour Adults: 1 hour	Vd: 0.22 to 0.87 L/kg Protein binding: >99%	Hepatic by n-dealkylation and aliphatic and aromatic hydroxylation to at least three metabolites: Triazoledione, hydroxynefazodone (active), and m-chlorophenylpiperazine (mCPP; active)	Primarily urine (~55%; as metabolites); feces (~20% to 30%)	Children: 4.1 hours Adolescents: 3.9 hours Adults: Parent drug: 2 to 4 hours; active metabolites: 1.4 to 8 hours

Agent	Action	Distribution	Metabolism	Excretion	Half-life elimination
Trazodone	Absorption: Well absorbed; Extended release: C_{max} increases ~86% when taken shortly after ingestion of a high-fat meal compared to fasting conditions Onset of action: Therapeutic (antidepressant): Up to 6 weeks; sleep aid: 1 to 3 hours Time to peak, serum: 30 to 100 minutes; delayed with food (up to 2.5 hours)	V_D: ~0.84 L/kg Protein binding: 85% to 95%	Hepatic via CYP3A4 (extensive) to an active metabolite (mCPP)	Primarily urine (74%, <1% excreted unchanged); secondarily feces (~21%)	5 to 9 hours, prolonged in obese patients
Vilazodone	Bioavailability: 72% (with food); blood concentrations (AUC) may be decreased ~50% in the fasted state Time to peak, serum: 4 to 5 hours	V_D: unknown Protein binding: ~96% to 99%	Extensively hepatic, via CYP3A4 (major pathway) and 2C19 and 2D6 (minor pathways)	Urine (1% as unchanged drug); feces (2% as unchanged drug)	~25 hours
Vortioxetine	Bioavailability: 75% Time to peak: 7-11 hours	V_D: 0.26 L/kg Protein binding: 98%	Hepatic primarily through oxidation via CYP450 isoenzymes, primarily CYP2D6, and subsequent glucuronic acid conjugation to an inactive carboxylic acid metabolite	Urine (59%); feces (26%)	~66 hours

Agent	Action	Distribution	Metabolism	Excretion	Half-life elimination
Central Nervous System Agents					
Atomoxetine	Absorption: Rapid Bioavailability: 63% in extensive metabolizers; 94% in poor metabolizers Time to peak, plasma: 1-2 hours; delayed 3 hours by high-fat meal	V_D: IV: 0.85 L/kg Protein binding: 98%, primarily albumin	Hepatic, via CYP2D6 and CYP2C19; forms metabolites (4-hydroxyatomoxetine, active, equipotent to atomoxetine; N-desmethylatomoxetine, limited activity); Note: CYP2D6 poor metabolizers have atomoxetine AUCs that are ~10-fold higher and peak concentrations that are ~fivefold greater than extensive metabolizers; 4-hyroxyatomoxetine plasma concentrations are very low (extensive metabolizers: 1% of atomoxetine concentrations; poor metabolizers: 0.1% of atomoxetine concentrations	Urine (80%, as conjugated 4-hydroxy metabolite; <3% is excreted unchanged); feces (17%)	5 hours (up to 24 hours in poor metabolizers); Active metabolites: 4-hydroxyatomoxetine: 6-8 hours; N-desmethylatomoxetine: 6-8 hours (34-40 hours in poor metabolizers)
Antimanic Agents					
Lithium	Absorption: Rapid and complete Bioavailability: 80% to 100% Time to peak, serum: Immediate release: ~0.5 to 3 hours; Extended release: 2 to 6 hours; Solution: 15 to 60 minutes	V_D: Initial: 0.307 L/kg; V_{Dss}: 0.7 to 1 L/kg; decreased in elderly patients Protein binding: Not protein bound	Not metabolized	Urine (primarily; unchanged drug); sweat, saliva, and feces (negligible amounts)	18 to 36 hours; prolonged in elderly patients (~28.5 hours) Clearance: 80% of filtered lithium is reabsorbed in the proximal convoluted tubules; decreased in elderly patients secondary to age-related decreases in renal function

Key: Tmax: time to max concentration; BA: bioavailability; Pb: protein binding; V_D: volume of distribution; IM: intramuscular; ER: extended release; IR: immediate release, V_{Dss}: volume of distribution at steady state; CYP: cytochrome P450 (enzyme); AUC: area under the curve

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database, the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE, evaluating efficacy of the miscellaneous serotonergic agents are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Non-comparative and placebo-controlled trials and trials comparing monotherapy with combination regimens are excluded.[58-104] The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials that evaluated endpoints other than reduction of symptoms, such as pharmacologic characteristics,[105-109] adverse effects,[72,110-124] or quality-of-life.[91]
- Individual trials comparing the miscellaneous serotonergic agents in dose-finding studies or in healthy volunteers.[125-133]
- Individual clinical trials evaluating formulations or indications not currently approved in the US or clinical trials with unavailable reports.[86,97,134-159]

Clinical Efficacy

Atomoxetine

Atomoxetine is labeled for use in the treatment of ADHD.[9] An Oregon Health and Science University Drug Class Review on Pharmacological Treatments for ADHD was published in October 2009.[160] The drug class review includes a summary of the guideline recommendations, systematic reviews and comparative clinical trials evaluating the safety and efficacy of the agents. When evaluating treatments for ADHD, it is important to consider both patient age and dosage form. The Oregon Review evaluated studies in children, adolescents and adults. Studies in children favor efficacy compared to placebo with fair evidence for stimulant drugs and poor evidence for atomoxetine. Atomoxetine was compared to both immediate release and extended release stimulants. The evidence weakly suggests that atomoxetine is comparable in efficacy to immediate release stimulants and inferior to extended release formulations. Fewer studies have been done in adolescents than in younger children. The level of evidence in these studies is poor, but the efficacy of different agents appears to follow the same trends as in children. The efficacy of atomoxetine was not consistently superior to placebo in adults.

One Cochrane Review and five additional systematic reviews and meta-analyses evaluating the efficacy of atomoxetine have been published since 2009. Pringsheim et al[161] published a Cochrane Review of pharmacological treatments for ADHD in children with comorbid tic disorders in 2011. The review identified and evaluated 8 randomized controlled trials. According to the available evidence, atomoxetine, clonidine, desipramine, dextroamphetamine, guanfacine and methylphenidate were efficacious in treating symptoms of ADHD. Guanfacine, desipramine, methylphenidate, clonidine and the combination of methylphenidate and clonidine were also efficacious in reducing tic symptoms. High-dose methylphenidate and high-dose dextroamphetamine may be associated with worsening tic symptoms.

Cunill et al[162] published a systematic review evaluating the efficacy of atomoxetine in adult patients with ADHD in 2013. Twelve studies of 3,375 patients were identified for evaluation. According to the analysis, atomoxetine therapy was associated with increased treatment discontinuation rates compared to placebo. A second systematic review of 5 randomized controlled trials and 10 open-label extension studies of 3,176 adult patients with ADHD was published in 2012.[163] Methylphenidate agents, amphetamine agents and atomoxetine were all found to be more efficacious than placebo but no differences in efficacy were reported between treatment groups. Adverse events reported with atomoxetine therapy included increased blood pressure, increased heart rate, dizziness, nausea, dry mouth, fatigue, decreased appetite, urinary hesitation and erectile dysfunction.

The safety and efficacy of atomoxetine therapy in pediatric patients was evaluated in a meta-analysis of 25 double-blind randomized controlled trials (2014). Schwartz et al,[164] reported increased rates of efficacy (reduced ADHD symptoms) as well as improved quality-of-life and reduced oppositional defiant disorder symptoms with atomoxetine therapy compared to placebo. Gastrointestinal, central nervous system (CNS), anorexia and fatigue were reported more frequently with atomoxetine therapy although no differences in the rate of serious adverse events were reported between the treatment group and placebo. Roskell et al,[165] published a systematic review and meta-analysis of 32 randomized controlled trials evaluating the efficacy of methylphenidate, dexamphetamine and atomoxetine in children with ADHD (2014). According to the analysis, lisdexamfetamine therapy may be more effective in reducing ADHD symptoms than atomoxetine but may also be associated with increased adverse-event discontinuation rates. Another large meta-analysis of 28 randomized, controlled trials evaluating the efficacy of ADHD treatments in pediatric patients was published in 2015.[166] According to this analysis, lisdexamfetamine therapy was associated with high rates of efficacy (reducing symptoms) while atomoxetine and methylphenidate were associated with moderate rates of efficacy and bupropion therapy was associated with low rates of efficacy. Lisdexamfetamine therapy was associated with the highest treatment discontinuation rates compared to the other treatment groups.

Overall, atomoxetine is more effective than placebo in the treatment of ADHD in children, but evidence comparing atomoxetine to other treatments is inconsistent and suggests reduced rates of efficacy for atomoxetine across all treatment age groups.

<u>Bupropion</u>

Bupropion is labeled for use in the treatment of depression, SAD, and smoking cessation. Six Cochrane Reviews, one Cochrane update, six additional systematic reviews & meta-analyses and one comparative clinical trial (bupropion vs trazodone) are available for evaluation of bupropion therapy.

Gartlehner et al[167] published a Cochrane Review of second-generation antidepressants in the treatment of seasonal affective disorder in adults. A total of only 4 clinical trials (n=1,100) were identified for evaluation. According to the limited evidence, bupropion XL demonstrated efficacy in the prevention of depressive episodes in patients with SAD but was associated with increased rates of headache, insomnia and nausea compared to placebo. A Cochrane update including two new reports and review of 11 others evaluating interventions used in smoking cessation was published in 2013.[103] According to the update, adding mood management (with

bupropion, a tricyclic antidepressant, selective serotonin inhibitor, etc.) to behavioral support (group therapy, individual counseling, internet/phone-based interventions, etc.) increases treatment success in patients with current or past depression. In addition, the update confirms evidence for the safety of bupropion and varenicline and the benefits of behavioral support in pregnancy. In 2015, Coleman et al,[168] published a Cochrane Review evaluating smoking cessation therapies in pregnancy. According to the evidence, nicotine replacement therapy with behavioral support is efficacious in reducing smoking during pregnancy; however, the safety of this intervention is not well understood. Insufficient evidence is available to determine the fetal impacts of either bupropion or varenicline in pregnancy. In 2013, Tsoi et al,[169] published a Cochrane Review evaluating smoking cessation therapies in patients with schizophrenia. According to the evidence, treatment with bupropion leads to increased rates of smoking abstinence without jeopardizing the mental state of patients with schizophrenia while treatment with varenicline lead to increased rates of smoking abstinence with mixed effects on mental state. No reports of serious adverse events including seizures were reported with bupropion treatment.

A 2015 Cochrane Review evaluating interventions for smokeless tobacco use cessation reported varenicline, nicotine lozenges and behavioral support are also efficacious in this patient population.[170] According to limited evidence, pooled results from two bupropion clinical trials did not demonstrate continued efficacy at six months. A Cochrane Review of antidepressants for smoking cessation published in 2014 reported bupropion and nortriptyline are efficacious in long-term smoking cessation.[171] Adverse events reported with bupropion and nortriptyline are rarely serious or lead to discontinuation. According to the report, both SSRIs (e.g. fluoxetine) and MAOIs fail to demonstrate efficacy in smoking cessation. In addition, a Cochrane Review of interventions for waterpipe smoking cessation was published in 2015 (and subsequent non-Cochrane Review update published 2016).[172,173] According to the evidence, two clinical trials demonstrated significantly higher quit rates in treatment groups receiving bupropion with behavioral support compared to placebo.

A review of smoking cessation intervention reviews was completed in 2015 for the U.S. Preventive Services Task Force.[174] According to the report, behavioral support, nicotine replacement therapy, bupropion and varenicline demonstrated efficacy for smoking cessation. Behavioral therapy in combination with pharmacotherapy increased cessation rates by 82% compared to minimal intervention or usual care. Electronic cigarettes did not demonstrate efficacy and none of the pharmacological interventions were associated with cardiovascular adverse effects. Weiner et al[175] published a meta-analysis of four clinical studies evaluating the efficacy of bupropion SR when added to group therapy for smoking cessation in patients with schizophrenia. According to the analysis, bupropion is tolerable and efficacious in the treatment of cigarette smoking in schizophrenia when compared to placebo.

Maneeton et al[176] published a small meta-analysis of 3 randomized, controlled trials (n=1117) evaluating the efficacy and venlafaxine and bupropion in the treatment of depression. According to the limited evidence, bupropion XL demonstrated similar rates of safety and efficacy as venlafaxine XR in adult patients with major depressive disorder. Two additional analyses of bupropion in the treatment of depression are available. A pooled analysis of 7 double-blind, randomized, controlled trials evaluating the efficacy of bupropion and SSRIs in the treatment of depression was published in 2007.[177] According to the report, no differences in response time and

remission rate were reported between bupropion and SSRI treatment groups. A second pooled analysis of ten double-blind, randomized studies evaluating the efficacy of bupropion and SSRIs in the treatment of concurrent depression with anxiety was published in 2008.[178] According to the report, response rates were increased with SSRI therapy compared to bupropion therapy in the treatment of anxious depression (65.4% vs. 59.4%, p=0.03). No differences in efficacy were reported between the treatment groups in patients with depression and moderate to low levels of anxiety. One meta-analysis evaluating the efficacy of bupropion in the treatment of SSRI-resistant depression is available. Papakostas et al,[179] published the analysis of four clinical trials (n=1496) in 2008. According to the report, patients switched to a non-SSRI antidepressant (bupropion, mirtazapine, venlafaxine) demonstrated increased remission rates compared to those switched to a second SSRI (28.0% vs 23.5%, p=0.007). No differences in efficacy were reported between the individual non-SSRI agents.

A large meta-analysis of 28 randomized, controlled trials evaluating the efficacy of ADHD treatments in pediatric patients was published in 2015.[166] According to this analysis, lisdexamfetamine therapy was associated with high rates of efficacy (reducing symptoms) while atomoxetine and methylphenidate were associated with moderate rates of efficacy and bupropion therapy was associated with low rates of efficacy. Lisdexamfetamine therapy was associated with the highest treatment discontinuation rates compared to the other treatment groups. A systematic review of meta-analyses evaluating the efficacy of pharmacotherapy and psychotherapy in the treatment of ADHD in adults was published in 2013.[180] Moriyama et al. reported increased rates of efficacy with bupropion therapy when compared to placebo but reduced rates of efficacy when compared to stimulants.

Bupropion was compared to trazodone in one double-blind, randomized, controlled trial of 124 patients with moderate-severe depression. Weisler et al[181] randomized patients to receive either bupropion 225-450 mg/day (n=63) or trazodone 150 to 400 mg/day (n=61) for 6 weeks. At the end of the study period, symptoms were improved 58% in the bupropion treatment group and 46% in the trazodone treatment group and weight changes were reported as a 2.5 lb loss in the bupropion treatment group and 1.2 lb gain in the trazodone treatment group (p=NS for both outcomes). Increased rates of anorexia and anxiety were reported in the bupropion treatment group and increased rates of somnolence and edema were reported in the trazodone treatment group (p<0.05).

Overall, this evidence suggests bupropion may be an effective treatment option in patients with depression, drug-resistant depression, seasonal affective disorder and smoking cessation.

<u>Lithium</u>

Lithium is labeled for use in the treatment of bipolar disorder. Three Cochrane Reviews and four additional systematic reviews and meta-analyses evaluating the efficacy of lithium are available for evaluation.

One Cochrane Review evaluating the efficacy of lithium in the maintenance treatment of mood disorders was published in 2001. Burgess et al[182] evaluated nine studies (n=825) comparing lithium to placebo. According to the evidence, lithium therapy was associated with reduced rates of relapse in bipolar disorder when compared to placebo. In addition, social functioning and

general health improved in the lithium treatment groups. A second Cochrane Review evaluating the comparative efficacy of lithium in the long-term treatment of unipolar affective disorder was published in 2006. Cipriani et al,[183] evaluated eight trials (n=475) comparing lithium to antidepressant therapy. Similar to the previous review, lithium therapy reduced rates of relapse (both depressive and manic) when compared to antidepressant therapy ($p<0.05$). No other significant differences in any outcomes were reported between treatment groups including quality-of-life, social functioning, occupational functioning and drop-out rates. A third Cochrane Review evaluating the efficacy of lithium in the treatment of schizophrenia was updated in 2015. Leucht et al,[184] evaluated 22 studies (n=763) comparing lithium to placebo or other antipsychotic therapies. Most included studies were small and of short duration. Lithium therapy demonstrated no improvements when compared to placebo or other antipsychotic agents. Augmentation of antipsychotic therapy with lithium increased rates of efficacy when compared to antipsychotic therapy alone (no *p*-value reported). No significant differences in adverse events were reported between treatment groups; however, the adverse event data was limited to very few studies.

A systematic review and meta-analysis evaluating the efficacy of lithium in the prevention of mood episodes in bipolar disorders was published in 2014. Severus et al,[185] evaluated seven trials (n=1,580) comparing lithium to placebo. According to the evidence, lithium therapy demonstrated increased rates of efficacy (defined as preventing overall mood episodes, both manic and depressive) when compared to placebo. When compared to anticonvulsant therapy, lithium therapy demonstrated increased rates of preventing manic episodes but no differences in preventing depressive or overall frequency of any episode. A meta-analysis evaluating the efficacy of lithium in acute bipolar depression was published in 2014. Selle et al,[186] evaluated 24 trials including 10 different treatments including: aripiprazole (2 trials), carbamazepine (1 trial), lamotrigine (5 trials), lithium (1 trial), lurasidone (1 trial), olanzapine (2 trials), olanzapine-fluoxetine (1 trial), quetiapine (5 trials), valproate (4 trials) and ziprasidone (2 trials). Pooled evidence reported efficacy ranked as follows: olanzapine + fluoxetine ≥ valproate > quetiapine > lurasidone > olanzapine, aripiprazole, carbamazepine. Ziprasidone therapy was found to be ineffective and lithium therapy is inadequately studied.

A systematic review and meta-analysis evaluating the efficacy of lithium in the prevention of suicide in mood disorders was published in 2013. Cipriani et al,[187] evaluated 48 randomized controlled trials (n=6674 participants, 15 comparisons). According to the evidence, lithium therapy was associated with reduced number of suicides (odds ratio [OR] 0.13, 95% confidence interval [CI] 0.03 to 0.66) and deaths from any cause (OR 0.38, 95% CI 0.15 to 0.95) when compared to or other active comparators (amitriptyline, carbamazepine, valproate, fluoxetine, fluvoxamine, imipramine, lamotrigine, mianserin, maprotiline, nortriptyline, olanzapine, phenelzine, quetiapine, thyroid hormone). In addition, lithium therapy was evaluated in the augmentation of tricyclic and second-generation antidepressants in major depression in a systematic review and meta-analysis published in 2014. Nelson et al[188] evaluated 9 trials (n=237) and reported increased rates of treatment response when lithium was added to either a TCA or second-generation agent. Adverse event discontinuation rate with lithium therapy did not differ from placebo.

This evidence suggests lithium therapy is an effective treatment option in bipolar disorder and may also be effective in the treatment of refractory depression or schizophrenia.

Mirtazapine

Mirtazapine is labeled for use in the treatment of depression. One Cochrane Review, 3 additional systematic reviews and meta-analyses, 1 clinical review and 1 comparative clinical trial (mirtazapine vs trazodone) evaluating the efficacy of mirtazapine are available for evaluation.

One Cochrane Review evaluating the efficacy of mirtazapine in the treatment of depression was published in 2011. Watanabe et al[100] evaluated 29 randomized controlled trials (n=4,974) comparing mirtazapine to other antidepressant agents. When compared to SSRIs, (12 trials, n=2,626) or to SNRIs (2 trials, n=415), mirtazapine therapy demonstrated significantly higher rates of efficacy. Evidence was insufficient to determine the clinical efficacy of mirtazapine compared to a TCA or to determine differences in treatment drop-out rates. Adverse even rates varied between treatment groups; mirtazapine therapy was associated with higher rates of weight gain and somnolence while SSRIs were associated with higher rates of nausea, vomiting and sexual dysfunction.

A systematic review and meta-analysis evaluating the efficacy of mirtazapine in the short-term treatment of depression was published in 2001. Bech et al[60] evaluated seven trials (n=665) comparing mirtazapine to amitriptyline or placebo. According to the evidence, both mirtazapine and amitriptyline are more effective than placebo in reducing symptoms associated with major depression. In addition, both agents demonstrated early onsets of action compared to placebo. A second meta-analysis evaluating the efficacy of mirtazapine in the treatment of major depressive disorder was published in 2008. Papakostas et al,[189] evaluated 10 randomized, controlled trials (n=1,904) comparing mirtazapine to SSRIs. No differences in clinical response or discontinuation rates were reported between treatment groups. Differences in adverse events were reported between the agents with higher rates of fatigue, weight gain and dry mouth reported in the mirtazapine treatment groups and higher rates of insomnia and nausea in the SSRI treatment groups ($p<0.05$ for all differences). A third meta-analysis evaluating the efficacy of mirtazapine in the acute phase treatment of depression was published in 2010. Thase et al[97] evaluated the efficacy of mirtazapine (N=1,484) compared to SSRIs (N=1,487) in 15 clinical trials. According to the evidence, mirtazapine therapy was associated with higher remission rates and faster time to remission compared to the SSRI agents ($p<0.05$). Comparative safety data was not provided in the review.

A clinical review of the evidence available evaluating the efficacy of mirtazapine was published in 2013. Alam et al[190] evaluated 293 trials (n>2,000) to determine the therapeutic efficacy of mirtazapine in a number of psychiatric and medical conditions. According to the evidence, mirtazapine has a unique mechanism of action and demonstrates efficacy as an antidepressant with a rapid onset of action and high response/remission rates. Of note, mirtazapine therapy has demonstrated efficacy in the treatment of depression in special populations including treatment-resistant disease, geriatric depression, anxious depression and agitation. Evidence also suggests mirtazapine may be efficacious in the treatment of various neurologic conditions, insomnia, nausea/vomiting and pain. Two meta-analyses evaluating the efficacy of mirtazapine as add-on treatment to antipsychotic therapy for negative symptoms in patients with chronic schizophrenia are available. Vidal et al[98] evaluated 5 studies and reported significantly improved negative symptoms in patients with schizophrenia with adjuvant mirtazapine therapy ($p<0.05$). Phan et al[147] evaluated six studies and reported the outcome of improved negative symptoms with

adjuvant mirtazapine therapy is limited by short study duration and small sample sizes. A third meta-analysis[191] evaluating the efficacy of mirtazapine in schizophrenia patients provided evidence in support of mirtazapine as a treatment for antipsychotic-induced akathisia, particularly in patients with contraindications to beta-blocker therapy or in patients with comorbid depression or negative symptoms.

Mirtazapine was compared to trazodone in one double-blind, randomized, controlled trial of 200 hospitalized patients with moderate-severe depression. Von Moffaert et al[192] randomized patients to receive either mirtazapine 24-72 mg/day (n=100) or trazodone 150 to 400 mg/day (n=100) for 6 weeks. At the end of the study period, mirtazapine therapy demonstrated higher rates of efficacy (defined as a reduction in depressive symptoms and increased remission rates) compared to trazodone therapy. With regard to adverse events, trazodone was associated with higher rates of somnolence and postural symptoms when compared to mirtazapine.

This evidence suggests mirtazapine is an effective treatment option for patients with depression. In addition, mirtazapine may be effective in the treatment of depression in special populations and the evidence suggests mirtazapine therapy maybe more efficacious than SSRIs and trazodone.

Nefazodone

Nefazodone is labeled for use in the treatment of depression. Two meta-analyses and 1 clinical review evaluating the efficacy of nefazodone are available for evaluation.

One systematic review and meta-analysis evaluating the efficacy of nefazodone in the treatment of anxiety and agitation in patients with depression was published in 1995. Fawcet et al[140] evaluated 6 randomized, double-blind trials (n=817) comparing nefazodone (n=184) to imipramine (n=288) or placebo (n=345). According to the evidence, both nefazodone and amitriptyline are more effective than placebo in reducing symptoms associated with major depression. Nefazodone also demonstrated significantly greater improvement in somatic anxiety compared to placebo, more rapid improvement in agitation compared to both imipramine and placebo and a low adverse event rate (5%) compared to imipramine (17%) and placebo (5%). One meta-analysis evaluating the efficacy of nefazodone in the treatment of major depression was published in 2007. Papakostas et al[193] evaluated 9 studies (n=988) comparing the efficacy of nefazodone or trazodone compared to SSRIs. Overall, no differences in efficacy, discontinuation rates or adverse events were reported between nefazodone/trazodone treatment groups and SSRI treatment groups.

A clinical review of the evidence available evaluating the efficacy of nefazodone was published in 1996. Cyr et al[74] evaluated double-blind, placebo-controlled studies to determine the pharmacokinetics, efficacy, safety and drug interactions of nefazodone. Based on the comparative evidence, nefazodone (>300 mg/day) was associated with increased rates of efficacy compared to placebo and similar rates of efficacy to imipramine. Nefazodone treatment was associated with a reduced adverse event rate compared to TCAs, a reduced rate of sexual dysfunctions compared to SSRIs and a reduced rate of dizziness compared to placebo trazodone.

The limited clinical evidence evaluating the efficacy of nefazodone suggests nefazodone is an effective treatment option for patients with depression.

Trazodone

Trazodone is labeled for use in the treatment of depression. Three systematic reviews and meta-analyses and 2 comparative clinical trials (trazodone vs bupropion and trazodone vs mirtazapine) evaluating the efficacy of trazodone are available for evaluation.

One meta-analysis evaluating the efficacy of trazodone in the treatment of depression was published in 1992. Patten et al[194] evaluated 6 studies comparing trazodone to imipramine. According to the evidence, trazodone and imipramine demonstrate similar rates of efficacy on the treatment of depression. Adverse event data was not provided in the review. A second meta-analysis evaluating the efficacy of trazodone in the treatment of depression was published in 1993. Workman et al[195] evaluated studies comparing imipramine, trazodone, bupropion and fluoxetine. According to the evidence, all of the agents are more efficacious than placebo in reducing depression symptoms. No differences in efficacy were reported between active treatment groups. A third meta-analysis evaluating the efficacy of trazodone in the treatment of major depression was published in 2007. Papakostas et al[193] evaluated nine studies (n=988) comparing the efficacy of nefazodone or trazodone compared to SSRIs. Overall, no differences in efficacy, discontinuation rates or adverse events were reported between nefazodone/trazodone treatment groups and SSRI treatment groups.

Trazodone was compared to bupropion in one double-blind, randomized, controlled trial of 124 patients with moderate-severe depression. Weisler et al[181] randomized patients to receive either bupropion 225-450 mg/day (n=63) or trazodone 150 to 400 mg/day (n=61) for 6 weeks. At the end of the study period, symptoms were improved by 58% in the bupropion treatment group and 46% in the trazodone treatment group and weight changes were reported as a 2.5 lb loss in the bupropion treatment group and 1.2 lb gain in the trazodone treatment group (p=NS for both outcomes). Increased rates of anorexia and anxiety were reported in the bupropion treatment group and increased rates of somnolence and edema were reported in the trazodone treatment group ($p<0.05$).

Trazodone was compared to mirtazapine in one double-blind, randomized, controlled trial of 200 hospitalized patients with moderate-severe depression. Von Moffaert et al[192] randomized patients to receive either mirtazapine 24-72 mg/day (n=100) or trazodone 150 to 400 mg/day (n=100) for 6 weeks. At the end of the study period, mirtazapine therapy demonstrated higher rates of efficacy (defined as a reduction in depressive symptoms and increased remission rates) compared to trazodone therapy. With regard to adverse events, trazodone was associated with higher rates of somnolence and postural symptoms when compared to mirtazapine.

Clinical evidence evaluating trazodone in off-label indications, including insomnia, are also available for evaluation. Two Cochrane Reviews and four other systematic reviews and meta-analyses were identified for evaluation.

Seitz et al[150] published a Cochrane Review of antidepressant therapy in the treatment of agitation and psychosis associated with dementia. A total of nine clinical trials (n=692) were

identified for evaluation. Sertraline and citalopram demonstrated improved outcomes while insufficient evidence is available to determine the efficacy of trazodone in this patient population. According to the limited evidence, trazodone appears to have a reduced adverse event rate compared to placebo and antipsychotic agents. McCleery et al[155] published a Cochrane Review of treatments for sleep disturbances in Alzheimer's disease. A total of only 5 clinical studies with melatonin, trazodone and/or ramelteon were identified for evaluation. According to the limited evidence, low-dose (50 mg) trazodone may be a safe and efficacious treatment option in this patient population while melatonin and ramelteon do not appear to be associated with the same benefit. More comparative clinical evidence is required to make specific recommendations for the treatment of sleep disturbances in Alzheimer's disease.

A clinical review of the evidence available evaluating the efficacy of trazodone in the treatment of insomnia was published in 2005. Mendelson et al[145] evaluated 18 clinical trials. Based on the available evidence, the efficacy of trazodone in insomnia is unknown. Most available studies are small and lack objective efficacy measures. In addition, a high adverse event discontinuation rate is reported with trazodone therapy due to sedation, dizziness, and psychomotor impairment. A systematic review evaluating the efficacy of trazodone in the treatment of insomnia in patients undergoing alcohol recovery was published in 2011. Kolla et al[196] evaluated 20 clinical trials including carbamazepine, chlormethiazole, gabapentin, melperone, quetiapine, ritanserin, scopolamine, topiramate, trazodone, triazolam and zopiclone. According to the evidence, trazodone has the most data (based on three studies) with improved efficacy (improved sleep measures) compared to placebo in 2 trials and similar rates of efficacy compared to gabapentin in 1 open-label trial. One meta-analysis evaluating the efficacy of trazodone in the treatment of pediatric headaches was published in 2013. El-Chammas et al[138] evaluated 21 clinical trials including clonidine, flunarizine, fluoxetine, pizotifen, propranolol, topiramate, trazodone and valproate. According to the evidence, both topiramate and trazodone demonstrated efficacy in reducing headache frequency compared to placebo. None of the other agents appeared to improve outcomes. A systematic review and meta-analysis evaluating the efficacy of trazodone in erectile dysfunction was published in 2003. Fink et al[141] evaluated 6 trials (n=396) and reported improved outcomes with trazodone in 3 of the included trials. According to the limited evidence, high-dose trazodone may be associated with increased rates of efficacy. Adverse-event rates were not significantly higher in the trazodone treatment groups compared to placebo; specific adverse events reported in the trazodone treatment groups include dizziness (16%), dry mouth (19%), fatigue (15%) and sedation (16%).

This evidence suggests trazodone is more effective than placebo and equally effective as imipramine and nefazodone in the treatment of depression. Trazodone is used in many off-labeled indications, of which the evidence for safety and efficacy is limited and a benefit-harm ratio is not well defined.

Vilazodone

Vilazodone is labeled for use in the treatment of depression. One systematic review and one clinical review were identified for evaluation of vilazodone therapy.

Citrome et al[70] evaluated the safety and efficacy profile of vilazodone in adult patients with major depressive disorder. Two randomized, double-blind trials (n=860) were identified for

evaluation. According to the limited evidence, vilazodone treatment is associated with increased rates of efficacy compared to placebo. The most frequently reported adverse events included diarrhea, nausea, vomiting and insomnia. No changes in sexual function or weight were reported in the studies. Wang et al[99] published a clinical evaluation of the same 2 randomized, double-blind trials and reported an earlier onset of action and absence of known cardiac adverse effects, which may be advantageous compared to other currently available antidepressant therapies. Comparative clinical trials are needed to determine the clinical utility of vilazodone therapy.

Vortioxetine

Vortioxetine is labeled for use in the treatment of depression. Five systematic reviews and meta-analyses were identified for evaluation of vortioxetine therapy.

Meeker et al[87] evaluated the safety and efficacy of vortioxetine in the treatment of acute depression. A total of 11 randomized, controlled trials (n=6,145) were identified for evaluation. According to the report, vortioxetine therapy is more efficacious than placebo but less efficacious than other SNRIs. The most frequently reported adverse effects with vortioxetine therapy were nausea and vomiting. No differences in efficacy but increased rates of adverse effects were reported with increasing doses of vortioxetine.

Pae et al[197] evaluated the efficacy of vortioxetine in the short-term treatment of major depressive disorder. Seven published and 5 unpublished randomized controlled trials (n=7,790) of short duration (6-12 weeks) were included in the analysis. Compared to placebo, vortioxetine therapy was associated with increased rates of response and remission. No differences in efficacy were reported between vortioxetine and SNRI therapy. The most frequent adverse events reported with vortioxetine therapy were nausea, vomiting, diarrhea and dry mouth. Adverse event discontinuation rates were lower in the vortioxetine treatment groups compared to SNRI treatment groups.

A second analysis by Pae et al[198] evaluated the efficacy of vortioxetine in the treatment of generalized anxiety disorder. A total of four short-term, randomized, placebo-controlled trials (n=606) were included in the analysis. According to the limited evidence, vortioxetine therapy is more efficacious than placebo. No differences in efficacy-related discontinuation rates were reported between treatment groups. Adverse event discontinuation rate was higher in the vortioxetine treatment group compared to placebo with significantly higher rates of nausea and dizziness in the active treatment group.

Berhan et al[199] evaluated the efficacy of vortioxetine in adult patients with major depressive disorder. A total of 7 randomized, double-blind trials (n=2,099) were included in the analysis. Vortioxetine therapy was associated with a ≥50% reduction in depressive symptoms when compared to baseline. No differences in comparative efficacy were reported when vortioxetine was compared to either placebo or active treatment (SNRI) therapy. Increased rates of adverse events were reported with vortioxetine therapy compared to placebo.

Fu et al[77] evaluated the efficacy of vortioxetine in treatment of major depressive disorder. Five randomized, placebo-controlled trials (n=1,700) were identified for evaluation. Compared to placebo, vortioxetine therapy reduced the rate of depressive symptoms. No differences in

remission rates were reported between vortioxetine and placebo treatment groups. The most frequently reported adverse events included diarrhea, dizziness, dry mouth, headache and nausea. Increased rates of nausea were reported in the vortioxetine treatment group compared to placebo. No differences in the rate of any other adverse events were reported between vortioxetine and placebo treatment groups.

Citrome et al[69] evaluated the safety and efficacy profile of vortioxetine in adult patients with major depressive disorder. Five published and 6 unpublished randomized controlled trials of short duration (6-8 weeks) were included in the analysis. According to the evidence, vortioxetine treatment was associated with increased rates of efficacy compared to placebo. The most frequently reported adverse events included constipation, nausea and vomiting.

This evidence suggests vortioxetine therapy is efficacious in reducing depressive symptoms and improving remission rates when compared to placebo in adult patients with major depressive disorder. Limited data is available for vortioxetine therapy compared to other antidepressant therapies and more clinical trials are needed to determine the comparative efficacy of vortioxetine therapy. Vortioxetine therapy may also be useful in the treatment of generalized anxiety disorder.

Safety

Black Box Warnings[1,2]: Bupropion, mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine and atomoxetine medications are labeled with a Black Box Warning. Use of these agents is associated with an increased risk of suicidal thoughts and behaviors in children, adolescents and young adults. Lithium labeling includes a Black Box Warning reminding prescribers that toxicity is related to serum levels, that that toxic levels occur at near therapeutic levels and toxic levels may not differ overlap and that the drug should be initiated only with the availability of lithium monitoring.

Warnings, Precautions and Adverse Events associated with use of the miscellaneous serotonergic agents may be reviewed in Tables 7 and 8 below.

Adverse Events:

Atomoxetine:

The most common adverse events associated with atomoxetine at an incidence greater than 10% include increased, headache, insomnia, drowsiness, hyperhidrosis, xerostomia, nausea, decreased appetite, abdominal pain, vomiting, constipation, erectile dysfunction, systolic/diastolic blood pressure elevations and tachycardia.[2,3]

Serious adverse events associated with atomoxetine use include myocardial infarction, sudden cardiac death, liver injury or failure, cerebrovascular accident, dyskinesia, seizure, mania, psychotic disorder, suicidal thoughts, priapism and angioedema.[2,3]

Dittmann et al[200] compared the efficacy and safety of lisdexamfetamine and atomoxetine in 267 children and adolescents with ADHD. Treatment emergent adverse events occurred at a similar rate with each treatment. Specifically, no differences were found between treatments for measures of diastolic or systolic blood pressure, pulse rate or weight reduction.

Reed et al[201] performed a comprehensive review of 7 safety topics associated with the use of atomoxetine in children and adolescents, including suicidality, aggression/hostility, psychosis/mania, seizures, hepatic effects, cardiovascular effects and growth/development. The review included 70 papers, the European Summary of Product Characteristics (SPC) and the US label. Suicidality with atomoxetine was associated with a hazard ratio of 0.96 in a large-register-based study. A second meta-analysis[111] found no significant association between atomoxetine and suicidality. A finding of aggression/hostility was not different in a meta-analysis comparing atomoxetine with placebo. Psychosis and activation of mania did occur in patients with comorbid bipolar disorder/depression. The 2-year seizure rate for atomoxetine in more than 2 million patients was 8 per 100,000 patients. The relationship of atomoxetine with liver disease/failure is unclear.[201] Up to 12% of pediatric patients may experience either small or more pronounced increases in heart rate or blood pressure on atomoxetine therapy. In long-term studies[201], discontinuations due to cardiovascular events were rare and most vital signs remain within the age norms. QTc interval prolongations of 1.4% were found during treatment of more than 3 years and not considered clinically significant. Overall, atomoxetine was not associated with clinically significant cardiovascular effects, aggression/hostility, growth reduction, seizures or suicidality.

A meta- and meta-regression analysis[164] compared the efficacy and tolerability of atomoxetine vs. placebo in children and adolescents with ADHD. Evidence from 25 double-blind, randomized, controlled trials (N=3928) were included. The all-cause discontinuation rate did not differ between atomoxetine and placebo therapy. Discontinuation rates were higher with atomoxetine due to adverse events and with placebo due to inefficacy. More patients receiving atomoxetine reported greater than one adverse event or psychiatric adverse event. No differences between groups were found for serious adverse events, aggression or suicidality.[164]

A second meta- and meta-regression analysis included 9 randomized, controlled trials (N=1828) found adverse events occurred more frequently in atomoxetine-treated patients with baseline hyperactivity/impulsive symptoms and included decreased appetite, abdominal pain, vomiting, dyspepsia, somnolence, dizziness, fatigue, sleep disturbances, infection and pruritus.[66]

<u>Bupropion:</u>

The most common adverse events associated with bupropion occurring at an incidence greater than 10% are tachycardia, headache, agitation, dizziness, insomnia, diaphoresis, weight loss, xerostomia, nausea, constipation, blurred vision and pharyngitis.[2,3]

Serious adverse events associated with bupropion use include complete atrioventricular block, myocardial infarction, colitis, pancreatitis, pancytopenia, abnormal liver function, hepatitis, jaundice, liver damage, anaphylactoid reaction, anaphylaxis, delayed hypersensitivity disorder, rhabdomyelosis, seizure, delusional disorder, worsening depression, hallucinations, hostile behavior, activation of hypomania/mania/psychosis, paranoid ideation, suicidality, pulmonary embolism and angioedema.[2,3]

The most common serious adverse event associated with bupropion use was seizures, occurring at a rate of 1 per 1000 users.[202] The risk of seizures was lower with use of SR vs IR products, at doses below 300 mg daily, in those without a personal or family history of seizures and without an underlying eating disorders.[202] In the setting of accidental or intentional overdose, 6% of subjects developed seizures, most commonly with the immediate release formulation.[203]

Cahill et al (2013) published a Cochrane Review that evaluated pharmacological interventions in smoking cessation.[202] They performed an overview and network meta-analysis of 82 trials (N= 7859) and found a small, but not statistically significant increase in adverse events with bupropion compared to placebo.[202] Bupropion use was associated with a 7-12% treatment-emergent adverse event dropout rate. Serious adverse events occurred in 2.5% bupropion-treated vs 2.2% placebo-treated patients. There were no differences between bupropion and placebo with regard to serious neuropsychiatric or cardiovascular adverse events. The meta-analysis was not robust enough to provide meaningful results with respect to the risk of bupropion-induced seizures. A total of 6 trials reported 8 seizures associated with bupropion use while placebo use did not produce any seizures.

A prospective comparative study evaluating fetal exposure during the first trimester of pregnancy was associated with a higher rate of spontaneous abortions.[204] In women giving birth, no fetal malformations were found.

Lithium:

The most common adverse events associated with lithium use at an incidence greater than 10% include acne, hypothyroidism, weight gain, gastritis, nausea, xerostomia, leukocytosis, fine tremor, deep tendon hyperreflexia, nephrotoxicity, polyuria, and increased thirst. [2,3]

Serious adverse events associated with lithium use include bradyarrhythmias, Brugada syndrome, sinus node dysfunction, reduction in peripheral circulation (transient), erythema multiforme, ataxia, coma, pseudotumor cerebri, increased intracranial pressure, papilledema, epileptiform seizure, blurred vision, tinnitus, giddiness, renal interstitial fibrosis and angioedema.[2,3]

Cipriani et al[183] performed a Cochrane Review of long-term treatment of unipolar or bipolar disorder with lithium or antidepressants. Their review of eight trials (N=475) found the overall adverse event rates did not differ between lithium and antidepressants; however, lithium use was associated more serious adverse effects (lithium toxicity, thyroid changes and renal dysfunction).

Cipriani et al[205] performed another Cochrane Review comparing valproic acid, valproate and divalproex to other mood stabilizers, antipsychotics or placebo therapy in the maintenance treatment of bipolar disorder. Five studies involving 838 participants were included. Lithium was associated with statistically more diarrhea, polyuria, increased thirst and enuresis, whereas valproate use produced significant increases in sedation and infection.

McKnight et al[124] performed a systematic review and meta-analysis involving 385 studies in which patients received lithium for treatment of mood disorders. The use of lithium was associated with a non-significant reduction in glomerular filtration rate of -6.22 mL/min. Urinary concentrating ability was significantly reduced by 15%. Thyroid use was statistically associated with clinical hypothyroidism, elevated levels of thyroid stimulating hormone (TSH) and increased levels of blood calcium and parathyroid hormone. Weight gain with lithium therapy was greater than with placebo but lower than with olanzapine therapy. No increased risk for congenital malformations, alopecia or skin disorders was found.

Mirtazapine:

The most common adverse events associated with mirtazapine use at an incidence greater than 10% include increased appetite, elevated triglycerides/cholesterol, weight gain, constipation, xerostomia and somnolence.[2,3]

Serious adverse events associated with mirtazapine use include agranulocytosis, neutropenia, liver cirrhosis, grand mal seizure, status epilepticus, exacerbation of depression, neuroleptic malignant syndrome, serotonin syndrome and suicidality.[2,3]

Watanabe et al[100] published a Cochrane Review that compared mirtazapine to other antidepressants in the treatment of depression. The review included 29 randomized, controlled trials (RCTs) involving 4974 participants. Dropout rates were similar among all agents. Mirtazapine produced significantly less hypertension, tachycardia and tremor than tricyclic antidepressants (TCAs). A response to therapy at two weeks was similar with mirtazapine and TCAs and more rapid than with SSRIs. In comparison to venlafaxine, mirtazapine use was more effective at both 2-weeks and end-of-therapy analyses. Compared with the SSRIs, mirtazapine use was associated with more weight gain and increased appetite and less nausea, vomiting and sexual dysfunction.

Nefazodone:

The most common adverse events associated with nefazodone use at an incidence greater than 10% include orthostatic hypotension, constipation, nausea, xerostomia, asthenia, confusion, dizziness, headache, lightheadedness, agitation, drowsiness, insomnia, somnolence, weakness and blurred vision.[2,3]

Serious adverse events associated with nefazodone use include electrocardiogram changes, Stevens-Johnson syndrome, neutropenia, hepatitis/liver failure, anaphylaxis, seizures (rarely), serotonin syndrome, exacerbation of depression, suicidal thoughts or behaviors, priapism and angioedema.[2,3]

A comparative study of nefazodone and paroxetine found headache and somnolence to be the most commonly reported adverse events in each treatment group at similar rates.[206] The manufacturer recommends initiating nefazodone therapy at low doses and titrating slowly to effective doses. A number of adverse events appear to be dose-related (e.g. somnolence, nausea, constipation, dizziness, vision changes, confusion, tinnitus) and to remit with continued use.[207,208] Benign abnormal vision changes (scotoma and palinopsia) appear to be dose-related and reversible with a dosage reduction. Compared to SSRIs (fluoxetine, paroxetine, and sertraline) nefazodone

demonstrated statistically less agitation and sexual dysfunction whereas SSRIs produced less dizziness, dry mouth and light-headedness.[208]

Insomnia and agitation are uncommon with nefazodone and occur at a rate comparable to placebo.[208] No differences were noted in tolerability in young vs elderly persons. Sexual dysfunction is uncommon. Nefazodone is not associated with weight gain. Nefazodone is associated with a lower rate of activation of mania/hypomania than tricyclic antidepressants (1.6% vs 5.1%). Nefazodone is not associated with the development of seizures. Rare cases of priapism have been reported; however, the low numbers do not allow for determination of causation. Nefazodone is not associated with serious cardiovascular effects. A potential for QT interval prolongation exists in combination with pimozide as nefazodone inhibits the metabolism and increases the serum concentrations of pimozide, further prolonging pimozide's effects on the QT interval. Nefazodone is not associated with a withdrawal syndrome. Nefazodone does not increase suicidality and is relatively safe in overdosage.[208]

Nefazodone was removed from the market in the European Union in 2003 due to hepatotoxicity concerns.[209] In the US, the FDA added a Black Box Warning to the label for Serzone®. Rare cases of liver failure some leading to transplant or death have been reported.[207] The onset of liver damage varied from 6 weeks to months after initiation of therapy. Abnormal hepatic enzyme abnormalities and liver biopsy indicate a non-immunologic, acute hepatitis with cholestasis and centrolobar necrosis. Systematic reviews estimated the incidence of nefazodone hepatotoxicity resulting in transplant or death to be 1 case per 250,000 to 300,000 patient-years of exposure. [210] It is believed that hepatotoxicity results from toxic intermediates produced during CYP3A4 metabolism of nefazodone. Routine monitoring of hepatic function is not recommended; however, patients should be evaluated for risk of hepatotoxicity (e.g. illicit drug use, alcohol consumption, exposure to other medications or hepatotoxins) and monitored for signs and symptoms of liver damage during therapy.[208]

Trazodone:

The most common adverse events associated with trazodone use at an incidence greater than 10% include nausea, xerostomia, dizziness, headache, somnolence, blurred vision, nervousness and fatigue. [2,3]

Serious adverse events associated with trazodone use include cardiac dysrhythmia, hypotension, prolonged QT interval, torsades de pointes, hypersensitivity reactions, seizure, serotonin syndrome, priapism and suicidality.[2,3]

Although trazodone has low anticholinergic activity, an increased risk of orthostatic hypotension in the elderly or those with heart disease may occur due to transient, concentration-dependent α_1-receptor antagonism.[145,211] The risk of falls or other injuries may be increased.[211] Trazodone interacts at the hERG potassium channel to prolong the QT interval. Life-threatening cardiac arrhythmias, including ventricular arrhythmias and torsade de pointes have occurred at both therapeutic and toxic concentrations.[145] Trazodone should not be used with other medications that prolong the QT interval or produce cardiac toxicity. Trazodone use has resulted in priapism rarely and males predisposed to priapism or with an anatomical malformation of the penis should not receive this drug. CYP3A4 enzyme inhibitors may increase the concentrations of trazodone

while enzyme inducers may reduce trazodone plasma concentration. Trazodone is not recommended for use concomitantly with TCAs, MAOIs or fluoxetine secondary to the risks of cardiotoxicity or serotonin syndrome. Trazodone, as with other antidepressants may increase the incidence of suicidality.[145,211]

A review of the safety of trazodone when used for insomnia found similar rates of side effects as when used in the treatment of depression. Up to 30% have difficulty tolerating trazodone in clinical trials, resulting in discontinuation of therapy due to adverse events (25%-50%). The adverse event profile of trazodone has not been well studied in insomnia patients who typically receive lower daily doses of trazodone than those with depression. Bedtime dosing of trazodone, 25-75 mg, resulted in a 31% discontinuation rate due to next-day sedation in patients receiving fluoxetine for depression.[145] Daytime somnolence was more common with trazodone 50 mg (23%) than placebo (8%) or zolpidem (16%).[36]

Vilazodone:

The most common adverse events associated with vilazodone use at an incidence greater than 10% include diarrhea, nausea, vomiting, and headache.[2,3]

Serious adverse events associated with vilazodone use include premature ventricular beats, abnormal bleeding, withdrawal syndrome, serotonin syndrome and suicidality. [2,3]

Laughrin et al[212] reviewed the FDA approval process for vilazodone, including raw clinical data sets submitted to the FDA, vilazodone clinical trial development data and the sponsors analysis. The incidence of serious adverse events in Phase 2 and 3 trials (8 trials, N=2177) submitted to the FDA were similar for vilazodone and placebo patients.[212] Discontinuations of vilazodone therapy due to adverse events were not above 1% for any single event and were most commonly reported for nausea, palpitations and fatigue. One patient receiving 80 mg daily and another who took an overdose of 240 mg vilazodone developed serotonin syndrome. Treatment emergent mania/hypomania was reported in 5 vilazodone- and 1 placebo-treated patient. The incidence of bleeding was 3% in both vilazodone and placebo treatment groups. In trials without active control, reporting of sexual dysfunction occurred more frequently with vilazodone although the incidence was low (<5%) and comparable to SSRIs. Vilazodone does not prolong the QT interval. In 5 patients who overdosed on vilazodone (200-280 mg) during Phase 2 and 3 trials, patients experienced serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation. Vilazodone has a narrow therapeutic range as maximal dosing is often associated with intolerable gastrointestinal adverse events.[79] Doses above 40 mg/day are not well tolerated by most patients.[212]

Vortioxetine:

The most common adverse event associated with vortioxetine use at an incidence greater than 10% is nausea. Although self-reporting of sexual dysfunction was low, scores on the Arizona Sexual Experience Scale did exceed 10% for both men and women.[2,3]

Serious adverse events associated with vortioxetine use include hyponatremia, abnormal bleeding, activation of mania/hypomania, serotonin syndrome and suicidality.[2,3]

Baldwin et al[213]performed a pooled analysis of the safety and tolerability of vortioxetine in the treatment of depression. Withdrawal due to an adverse events was most frequent with venlafaxine followed by duloxetine and vortioxetine. Nausea and vomiting occurred at similar rates among the 3 agents and appeared to be dose-related with vortioxetine. Compared with other antidepressants, vortioxetine was associated with a lower frequency of insomnia and sexual dysfunction.

Meeker et al[87] performed a systematic review and meta-analysis to evaluate the efficacy and harms associated with vortioxetine therapy. Discontinuation rates due to adverse events occurred more commonly with vortioxetine than SNRI or placebo treatment. Adverse events (vomiting, dizziness, hyperhidrosis, nasopharyngitis and fatigue) were significantly less common with vortioxetine 1 mg than an SNRI, however at a vortioxetine dose of 20 mg significant differences between treatment groups were found for hyperhidrosis. Serious adverse event rates did not differ at any dose.

Citrome et al[69] performed a systematic review evaluating the safety and efficacy of vortioxetine in the treatment of major depressive disorder. The frequency of nausea was dose-dependent, occurred early in therapy and more commonly in women.

Table 7. Warnings and Precautions for the Miscellaneous Serotonergic Agents[9,10]

	US Boxed Warnings	Warnings/Precautions	Other Considerations
Antidepressants			
Bupropion (Wellbutrin®; Wellbutrin® SR; Wellbutrin® XL; Zyban®)	Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders; consider risk prior to prescribing. Serious neuropsychiatric events have occurred in patients taking bupropion for smoking cessation. Contraindications: seizure disorder (and other conditions that increase seizure risk, including arteriovenous malformation, severe head injury, severe stroke, CNS tumor, CNS infection); history of anorexia/bulimia; patients undergoing abrupt discontinuation of ethanol or sedatives; use of MAOIs (concurrently or within 14 days), linezolid, intravenous methylene blue or multiple bupropion formulations	Use with caution in patients with hepatic impairment Use with caution in patients with renal impairment Use with caution in the elderly; may be at greater risk of drug accumulation during chronic dosing Bupropion is not FDA approved for bipolar depression	Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Extended release tablet: Insoluble tablet shell may remain intact and be visible in the stool Adverse events have been observed in some animal reproduction studies; Bupropion and its metabolites are excreted into breast milk
Mirtazapine (Remeron®; Remeron® SolTab™)	Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders; consider risk prior to prescribing. Contraindications: use of MAOIs (concurrently or within 14 days), linezolid or intravenous methylene blue	May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems May cause akathisia/psychomotor restlessness QT prolongation, torsade de pointes, and ventricular fibrillation have been reported (rarely)	Mirtazapine is not FDA approved for use in children Mirtazapine is not FDA approved for the treatment of bipolar depression Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Tablets contain lactose; SolTab formulation contains phenylalanine

	US Boxed Warnings	Warnings/Precautions	Other Considerations
		Use with caution in patients with hepatic impairment Use with caution in patients with renal impairment Use with caution in patients at risk of seizures	Adverse events were observed in some animal reproduction studies; Mirtazapine and its active metabolite are found in breast milk
Serotonin Modulators			
Nefazodone (Serzone®)	Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders; consider risk prior to prescribing. Cases of life-threatening hepatic failure have been reported. Discontinue if clinical signs or symptoms (such as increased serum AST or ALT levels greater than 3 times the upper limit of normal) suggest liver failure. Contraindications: active liver disease or elevated serum transaminases; concurrent use or use of MAOIs within previous 14 days; concurrent use with carbamazepine, cisapride or pimozide; concurrent therapy with triazolam is generally contraindicated	Use with caution in patients with renal impairment Use with caution in patients at risk of seizures May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention) May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin, or other anticoagulants	Nefazodone is not FDA approved for use in children Nefazodone is not FDA approved for the treatment of bipolar depression Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Adverse effects were observed in some animal reproduction studies; Nefazodone and its metabolites are excreted in breast milk
Trazodone (Desyrel®)	Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders; consider risk prior to prescribing. Contraindications: use of MAO inhibitors (concurrently or within 14 days), linezolid or intravenous methylene blue	Use with caution in patients with hepatic impairment Use with caution in patients with renal impairment Use with caution in patients at risk of seizures Use with caution in the elderly	Trazodone is not FDA approved for use in children Trazodone is not FDA approved for the treatment of bipolar depression Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy

	US Boxed Warnings	Warnings/Precautions	Other Considerations
		Although the risk of conduction abnormalities is low relative to other antidepressants, QT prolongation (with or without torsade de pointes) and ventricular tachycardia has been observed with the use of trazodone May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin, or other anticoagulants	Adverse effects were observed in some animal reproduction studies; Trazodone is excreted into breast milk
Vilazodone (Viibryd®)	Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders; consider risk prior to prescribing. Contraindications: use of MAO inhibitors (concurrently or within 14 days), linezolid or intravenous methylene blue	Use with caution in patients with a previous seizure disorder or condition predisposing to seizures such as brain damage or alcoholism May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin, or other anticoagulants	Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Adverse events have been observed in animal reproduction studies; It is not known if vilazodone is excreted in breast milk
Vortioxetine (Trintellix®)	Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders; consider risk prior to prescribing. Contraindications: use of MAO inhibitors (concurrently or within 14 days), linezolid or intravenous methylene blue	Use is not recommended in severe hepatic impairment Use with caution in patients with seizure disorders	The FDA has approved a brand name change for the antidepressant Brintellix (vortioxetine) to decrease the risk of prescribing and dispensing errors resulting from confusion with the blood-thinning medicine Brilinta (ticagrelor) Vortioxetine is not approved for use in children Vortioxetine is not FDA approved for the treatment of bipolar depression Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy

	US Boxed Warnings	Warnings/Precautions	Other Considerations
			Adverse events were observed in animal reproduction studies; It is not known if vortioxetine is excreted into breast milk
Central Nervous System Agents			
Atomoxetine (Strattera®)	Use with caution in pediatric patients; may be an increased risk of suicidal ideation. Contraindications: use with or within 14 days of MAO inhibitors; narrow-angle glaucoma; current or past history of pheochromocytoma; severe cardiac or vascular disorders in which the condition would be expected to deteriorate with clinically important increases in blood pressure (eg, 15 to 20 mm Hg) or heart rate (eg, 20 beats/minute)	New or worsening symptoms of hostility or aggressive behaviors have been associated with atomoxetine, particularly with the initiation of therapy Atomoxetine has been associated with serious cardiovascular events including sudden death in patients with preexisting structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke, and MI in adults) Use may be associated with rare but severe hepatotoxicity Use with caution in patients with a history of urinary retention or bladder outlet obstruction	Atomoxetine is not approved for major depressive disorder Adverse events have been observed in animal reproduction studies; It is not known if atomoxetine is excreted in breast milk
Antimanic Agents			
Lithium (Eskalith CR®; Eskalith®; Lithobid® Slow-release)	Lithium toxicity is closely related to serum concentrations and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy. Contraindications: avoid use in patients with severe cardiovascular or renal disease, or with severe debilitation, dehydration, or sodium depletion	Hypercalcemia with or without hyperparathyroidism has been reported Chronic therapy results in diminished renal concentrating ability (nephrogenic diabetes insipidus); this is usually reversible when lithium is discontinued Avoid use in patients with significant fluid loss or sodium depletion due to an increased risk of lithium toxicity	Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity (“gasping syndrome”) in neonates

	US Boxed Warnings	Warnings/Precautions	Other Considerations
		Avoid use in patients with significant renal disease due to an increased risk of lithium toxicity Use with caution in patients at risk of suicide Use with caution in patients with thyroid disease Generally, avoid use in severely debilitated patients due to an increased risk of lithium toxicity Use with caution in the elderly patients due to an increased risk of lithium toxicity	Adverse events have been observed in animal reproduction studies; Lithium is excreted in breast milk and serum concentrations of nursing infants may be 10% to 50% of the maternal serum concentration

Key: MDD – major depressive disorder: FDA – Food and Drug Administration; MAOI – monoamine oxidase inhibitor; ALT – alanine aminotransferase; AST – aspartate aminotransferase: NSAID – nonsteroidal anti-inflammatory drug; CNS – central nervous system

Table 8. Adverse Events Reported with the Miscellaneous Serotonergic Agents[9,10]

Adverse Effect	Bupropion (%)	Mirtazapine (%)	Nefazodone (%)	Trazodone (%)	Vilazodone (%)	Vortioxetine (%)	Atomoxetine (%)	Lithium (%)
Cardiovascular	Tachycardia (11%), Palpitations (2% to 6%), cardiac arrhythmia (5%), chest pain (3% to 4%), hypertension (2% to 4%; may be severe), flushing (1% to 4%), hypotension (3%)	Peripheral edema (2%), edema (1%), hypertension, vasodilatation	Bradycardia, hypotension, orthostatic hypotension, peripheral edema, vasodilation	Edema (≥1%)	Palpitations (1% to 2%)	NR	Headache (19%; children and adolescents), insomnia (1% to 19%), drowsiness (8% to 11%), Increased diastolic blood pressure (5% to 9%; ≥15 mm Hg), systolic hypertension (4% to 5%), palpitations (3%), cold extremities (1% to 3%), syncope (≤3%), flushing (≥2%), orthostatic hypotension (≤2%), tachycardia (≤2%), prolonged Q-T interval on ECG	Abnormal T waves on ECG, bradycardia, cardiac arrhythmia, chest tightness, circulatory shock, cold extremities, edema, hypotension, myxedema, sinus node dysfunction, startled response, syncope
Central Nervous System	Headache (25% to 34%), agitation (2% to 32%), dizziness (6% to 22%), insomnia (11% to 20%), Confusion (8%), anxiety (3% to 7%), hostility (6%), nervousness (3% to 5%), sensory disturbance (4%), sleep disorder (4%), migraine (1% to 4%), abnormal dreams (3%), memory impairment (≤3%), drowsiness (2% to 3%), irritability (2% to 3%), pain (2% to 3%), akathisia (≤2%), central nervous system stimulation (1% to 2%), paresthesia (1% to 2%), twitching (1% to 2%), depression	Drowsiness (54%), Dizziness (7%), abnormal dreams (4%), abnormality in thinking (3%), confusion (2%), agitation, amnesia, anxiety, apathy, depression, hypoesthesia, malaise, myasthenia, paresthesia, twitching, vertigo	Agitation, dizziness, drowsiness, headache, insomnia, Abnormal dreams, ataxia, chills, confusion, hypertonia, lack of concentration, memory impairment, paresthesia, psychomotor retardation	Sedation (46%), headache (33%), dizziness (25%), fatigue (15%), Agitation (≥1%), ataxia (≥1%), confusion (≥1%), disorientation (≥1%), memory impairment (≥1%), migraine (≥1%)	Headache (15%), Dizziness (6% to 8%), insomnia (6% to 7%), drowsiness (4% to 5%), fatigue (4%), abnormal dreams (3%), restlessness (2% to 3%), paresthesia (2%), delayed ejaculation (1% to 2%), migraine (≥1%), sedation (>1%), panic attack (≤1%), ventricular premature contractions (≤1%)	Female sexual disorder (self-reporting: 1% to 2%; Arizona Sexual Experience Scale: 22% to 34%), male sexual disorder (self-reporting: 3% to 5%; Arizona Sexual Experience Scale: 16% to 29%), Dizziness (8% to 9%), abnormal dreams (2% to 3%)	Fatigue (6% to 10%), dizziness (5% to 8%), depression (4% to 7%), disturbed sleep (3% to 7%), irritability (5% to 6%), jitteriness (2% to 5%), abnormal dreams (4%), chills (3%), paresthesia (adults 3%; postmarketing observation in children), anxiety (≥2%), hostility (children and adolescents 2%), emotional lability (1% to 2%), agitation, restlessness, sensation of cold	Ataxia, blackout spells, cogwheel rigidity, coma, confusion, dizziness, drowsiness, dystonia, EEG pattern changes, extrapyramidal reaction, fatigue, hallucination, headache, hyperactive deep tendon reflex, hypertonia, involuntary choreoathetoid movements, lethargy, local anesthesia, memory impairment, loss of consciousness, metallic taste, myasthenia gravis (rare), pseudotumor cerebri, psychomotor retardation, reduced intellectual ability, restlessness, salty taste, sedation, seizure, slowed intellectual functioning, slurred speech, stupor, tics, vertigo, worsening of organic brain syndromes

Adverse Effect	Bupropion (%)	Mirtazapine (%)	Nefazodone (%)	Trazodone (%)	Vilazodone (%)	Vortioxetine (%)	Atomoxetine (%)	Lithium (%)
Dermatologic	Diaphoresis (5% to 22%), Skin rash (1% to 8%), pruritus (2% to 4%), urticaria (1% to 2%)	Pruritus, skin rash	Pruritus, skin rash	Night sweats (≥1%)	Hyperhidrosis (≤1%), night sweats (≤1%)	Pruritus (2% to 3%)	Hyperhidrosis (4% to 15%), Excoriation (2% to 4%), skin rash (2%), pruritus, urticaria	Acne vulgaris, alopecia, blue-gray skin pigmentation, dermal ulcer, dry or thinning of hair, exacerbation of psoriasis, folliculitis, pruritus, psoriasis, skin rash, xerosis
Metabolic	Weight loss (14% to 23%), Weight gain (9%), menstrual disease (2% to 5%), decreased libido (3%), hot flash (1% to 3%)	Weight gain (12%; weight gain of >7% reported in 8% of adults, 49% of pediatric patients), increased serum cholesterol (15%), Increased serum triglycerides (6%), increased thirst	Decreased libido, increased thirst	Decreased libido (2%)	Decreased libido (2% to 4%), weight gain (2%)	NR	Weight loss (2% to 7%), decreased libido (3%), hot flash (3%), increased thirst (2%), menstrual disease	Hypothyroidism (females 14%; males 5% [Johnston 1999]), albuminuria, dehydration, diabetes insipidus, euthyroid goiter, glycosuria, hypercalcemia, hyperglycemia, hyperparathyroidism, hyperthyroidism, increased radioactive iodine uptake, increased thirst, polydipsia, weight gain, weight loss
Gastrointestinal	Xerostomia (17% to 28%), nausea (1% to 18%), Constipation (5% to 10%), abdominal pain (2% to 9%), diarrhea (5% to 7%), flatulence (6%), anorexia (3% to 5%), increased appetite (4%), dysgeusia (2% to 4%), vomiting (2% to 4%), dyspepsia (3%), dysphagia (≤2%)	Xerostomia (25%), increased appetite (17%), constipation (13%), Abdominal pain, anorexia, vomiting	Constipation, nausea, xerostomia, Diarrhea, dysgeusia, dyspepsia, gastroenteritis, increased appetite, vomiting	Xerostomia (25%), nausea (21%), Constipation (8%), abdominal pain (≥1%), dysgeusia (≥1%), vomiting (≥1%)	Diarrhea (26% to 29%), nausea (22% to 24%), Xerostomia (7% to 8%), abdominal pain (4% to 7%), vomiting (4% to 5%), dyspepsia (3%), flatulence (3%), increased appetite (3%), abdominal distension (2%), gastroenteritis (2%)	Nausea (dose-related, females >males, 21% to 32%; commonly occurs within the first week of treatment, then decreases in frequency but can persist in some patients), Diarrhea (7% to 10%), xerostomia (7% to 8%), constipation (5% to 6%), vomiting (3% to 6%), flatulence (2% to 3%)	Xerostomia (17% to 35%), nausea (7% to 26%), decreased appetite (15% to 23%), abdominal pain (7% to 18%), vomiting (4% to 11%), constipation (1% to 11%), Dyspepsia (4%), anorexia (3%), dysgeusia, flatulence	Abdominal pain, anorexia, dental caries, diarrhea, dysgeusia, dyspepsia, excessive salivation, flatulence, gastritis, nausea, vomiting, sialadenitis, sialorrhea, swelling of lips, xerostomia
Hematologic	NR	NR	Decreased hematocrit	NR	NR	NR	NR	Leukocytosis
Hepatic	NR	Increased serum ALT (≥3 times ULN: 2%)	NR	NR	NR	NR	NR	NR
Neuromuscular & skeletal	Tremor (3% to 6%), myalgia (2% to 6%), weakness (2% to 4%), arthralgia (1% to 4%), arthritis (≤2%), neck pain	Weakness (8%), back pain (2%), myalgia (2%), tremor (2%), arthralgia, hyperkinesia, hypokinesia	Weakness, Arthralgia, neck stiffness, tremor	Back pain (5%), myalgia (≥1%), tremor (≥1%)	Arthralgia (2%), tremor (>1%)	NR	Tremor (1% to 5%), muscle spasm, weakness	Joint swelling, muscle hyperirritability, neuromuscular excitability, polyarthralgia, tremor

Adverse Effect	Bupropion (%)	Mirtazapine (%)	Nefazodone (%)	Trazodone (%)	Vilazodone (%)	Vortioxetine (%)	Atomoxetine (%)	Lithium (%)
Ophthalmic/Otic	Blurred vision (2% to 15%), Tinnitus (3% to 6%), auditory disturbance (5%)	NR	Blurred vision (9%), visual disturbance (7%), eye pain, visual field defect, Tinnitus	Blurred vision (5%), visual disturbance (≥1%)	Blurred vision (≤1%), xerophthalmia (≤1%)	NR	Blurred vision (1% to 4%), conjunctivitis (1% to 3%), mydriasis	Blurred vision, exophthalmos, nystagmus, transient scotoma, Tinnitus
Renal	Urinary urgency (≤2%), vaginal hemorrhage (≤2%), urinary tract infection (≤1%), Polyuria (2% to 5%)	Urinary frequency (2%), urinary tract infection	Impotence, mastalgia, urinary frequency, urinary retention,	Ejaculatory disorder (2%), urinary urgency (≥1%)	Erectile dysfunction (≤3%), orgasm disturbance (1% to 2%)	NR	Erectile dysfunction (8% to 21%), Ejaculatory disorder (2% to 6%), urinary retention (1% to 6%), dysmenorrhea (3%), dysuria (2%), orgasm abnormal, pollakiuria, prostatitis, testicular pain, urinary frequency	Impotence, incontinence, oliguria
Respiratory	Pharyngitis (3% to 13%), Upper respiratory infection (9%), cough (1% to 4%), sinusitis (1% to 5%)	Flu-like symptoms (5%), dyspnea (1%), increased cough, sinusitis	Bronchitis, cough, dyspnea, flu-like symptoms, pharyngitis	Dyspnea (≥1%)	NR	NR	Pharyngolaryngeal pain	Decreased creatinine clearance, polyuria
Miscellaneous	<1%, postmarketing, and/or case reports (limited to life-threatening or important): Abnormal accommodation, aggressive behavior, akinesia, alopecia, amnesia, anaphylactic shock, anaphylactoid reaction, anemia, angioedema, angle-closure glaucoma, aphasia, ataxia, atrioventricular block, bronchospasm, bruxism, cerebrovascular accident, colitis, coma, cystitis, deafness, delayed hypersensitivity, delirium, delusions, depersonalization, derealization, diplopia, dysarthria, dyskinesia, dyspareunia, dysphoria, dystonia, dysuria, edema, EEG pattern changes, emotional lability, erythema multiforme, esophagitis, euphoria, exfoliative dermatitis,	<1%, postmarketing, and/or case reports: Abnormal accommodation, abnormal healing, abnormal hepatic function tests, abnormal lacrimation, acne vulgaris, ageusia, akathisia, alopecia, altered sense of smell, amenorrhea, anemia, angina pectoris, angle-closure glaucoma, aphasia, aphthous stomatitis, arthritis, asphyxia, asthma, ataxia, atrial arrhythmia, bigeminy, blepharitis, bone fracture, bone marrow depression (granulocytopenia, agranulocytopenia, aplastic anemia), bradycardia, breast engorgement, breast hypertrophy, bronchitis, bullous dermatitis, bursitis,	<1%, postmarketing, and/or case reports: Abnormal gait, abnormal hepatic function tests, abnormality in thinking, accommodation disturbance, acne vulgaris, ageusia, alopecia, amenorrhea, anemia, angina pectoris, angioedema, angle-closure glaucoma, anorgasmia, apathy, arthritis, asthma, atrioventricular block, attempted suicide, breast hypertrophy, bruise, bursitis, cardiac failure, cellulitis, cerebrovascular accident, colitis, conjunctivitis, convulsions, cystitis, deafness, dehydration, depersonalization, derealization, diplopia, disturbance in attention, dry eye syndrome, dysarthria, eczema, ejaculatory disorder, enlargement	<1%, postmarketing, and/or case reports: Abnormal dreams, abnormal gait, acne vulgaris, akathisia, alopecia, anemia, angle-closure glaucoma, anxiety, aphasia, apnea, atrial fibrillation, bladder pain, bradycardia, breast engorgement, breast hypertrophy, cardiac arrest, cardiac arrhythmia, cardiac conduction disturbance, cardiac failure, cerebrovascular accident, chills, cholestasis, diplopia, dry eye syndrome, erectile dysfunction, esophageal achalasia, extrapyramidal reaction, eye pain, flatulence, flushing, hallucination, hemolytic anemia, hirsutism, hyperbilirubinemia, hyperhidrosis, hypersensitivity,	<1%, postmarketing, and/or case reports: Angle-closure glaucoma, cataract, hallucination, hyponatremia, irritability, mania, seizure, serotonin syndrome, skin rash, suicidal ideation, suicidal tendencies, urticaria	<1%, postmarketing, and/or case reports: Angle-closure glaucoma, dysgeusia, dyspepsia, flushing, hypomania, hyponatremia, mania, seizure, serotonin syndrome, vertigo, withdrawal syndrome	<1%, postmarketing, and/or case reports: Aggressive behavior, akathisia, anaphylaxis, angioedema, cerebrovascular accident, change in libido, delusions, growth suppression (children), hallucination, hepatotoxicity, hypersensitivity reaction, hypoesthesia, hypomania, impulsivity, jaundice, lethargy, mania, myocardial infarction, panic attack, pelvic pain, priapism, Raynaud's phenomenon, rhabdomyolysis, seizure (including patients with no prior history or known risk factors for seizure), severe hepatic disease, suicidal ideation, tics	Fever, Angioedema

Adverse Effect	Bupropion (%)	Mirtazapine (%)	Nefazodone (%)	Trazodone (%)	Vilazodone (%)	Vortioxetine (%)	Atomoxetine (%)	Lithium (%)
	extrapyramidal reaction, extrasystoles, facial edema, gastric ulcer, gastroesophageal reflux disease, gastrointestinal hemorrhage, gingival hemorrhage, glossitis, glycosuria, gynecomastia, hallucination, hepatic injury, hepatic insufficiency, hepatitis, hirsutism, hyperglycemia, hyperkinesia, hypertonia, hypoesthesia, hypoglycemia, hypokinesia, hypomania, impotence, increased intraocular pressure, increased libido, intestinal perforation, jaundice, leukocytosis, leukopenia, lymphadenopathy, manic behavior, musculoskeletal chest pain, myasthenia, mydriasis, myocardial infarction, myoclonus, neuralgia, neuropathy, orthostatic hypotension, painful erection, pancreatitis, pancytopenia, paranoia, pneumonia, psychiatric signs and symptoms, pulmonary embolism, rhabdomyolysis, salpingitis, sciatica, seizure (dose-related), SIADH, skin photosensitivity, Stevens-Johnson syndrome, stomatitis, suicidal ideation, syncope, tardive dyskinesia, thrombocytopenia, tongue edema, urinary incontinence, urinary retention,vasodilatation	cardiac arrest, cardiomegaly, cellulitis, cerebral ischemia, chest pain, chills, cholecystitis, colitis, conjunctivitis, cystitis, deafness, dehydration, delirium, delusions, dementia, depersonalization, dermal ulcer, diabetes mellitus, diarrhea, diplopia, drug dependence, dysarthria, dyskinesia, dysmenorrhea, dystonia, dysuria, ejaculatory disorder, emotional lability, enlargement of abdomen, enlargement of salivary glands, eosinophilia, epistaxis, eructation, erythema multiforme, euphoria, exfoliative dermatitis, extrapyramidal reaction, eye pain, facial edema, fatigue, fever, gastritis, gastroenteritis, gingival hemorrhage, glaucoma, glossitis, goiter, gout, hallucination, headache, hematuria, hepatic cirrhosis, herpes simplex infection, herpes zoster, hiccups, hostility, hyperacusis, hyperreflexia, hypoesthesia (oral), hyponatremia,	of abdomen, epistaxis, eructation, esophagitis, euphoria, facial edema, galactorrhea, gastritis, gingivitis, gout, gynecomastia, halitosis, hallucination, hangover effect, heavy eyelids, hematuria, hemorrhage, hepatic failure, hepatic necrosis, hepatitis, hernia, hiccups, hostility, hyperacusis, hypercholesterolemia, hyperesthesia, hyperkinesia, hypermenorrhea, hypersensitivity reaction, hypertension, hyperventilation, hypoglycemia, hyponatremia, hypotonia, increased lactic dehydrogenase, increased libido, increased serum ALT, increased serum AST, increased serum prolactin, keratoconjunctivitis, laryngitis, leukopenia, lymphadenopathy, maculopapular rash, malaise, metrorrhagia, muscle rigidity, mydriasis, myoclonus, nephrolithiasis, neuralgia, neuroleptic malignant syndrome (Stevens, 2008), nocturia, nocturnal amblyopia, oliguria, oral candidiasis, oral mucosa ulcer, otalgia, pallor, paranoia, pelvic pain, peptic ulcer, periodontal abscess, photophobia, pneumonia, polyuria, priapism, rectal hemorrhage, rhabdomyolysis (with lovastatin/simvastatin), serotonin syndrome, sialorrhea, skin	hypersensitivity reaction, hypoesthesia, hypomania, hypotension, impotence, increased serum amylase, increased urine output, insomnia, jaundice, lack of concentration, lactation, leukocytosis, leukonychia, liver enzyme disorder, methemoglobinemia, muscle twitching, myocardial infarction, orgasm abnormal, orthostatic hypotension, palpitations, paranoia, paresthesia, photophobia, priapism, prolonged Q-T interval on ECG, pruritus, psoriasis, psychosis, reflux esophagitis, retrograde ejaculation, seizure, SIADH, sialorrhea, skin photosensitivity, skin rash, speech disturbance, stupor, syncope, tachycardia, tardive dyskinesia, tinnitus, torsades de pointes, urinary incontinence, urinary retention, urticaria, vasodilatation, ventricular ectopy, ventricular tachycardia, vertigo, vulvar pain, weakness				

Adverse Effect	Bupropion (%)	Mirtazapine (%)	Nefazodone (%)	Trazodone (%)	Vilazodone (%)	Vortioxetine (%)	Atomoxetine (%)	Lithium (%)
		hypotension, hypothyroidism, hypotonia, impotence, increased acid phosphatase, increased creatine phosphokinase, increased libido, increased serum AST, insomnia, intestinal obstruction, keratoconjunctivitis, laryngitis, left heart failure, lethargy, leukopenia, leukorrhea, lymphadenopathy, lymphocytosis, manic reaction, mastalgia, menorrhagia, migraine, mouth edema, myocardial infarction, myoclonus, myositis, nausea, neck pain, neck stiffness, nephrolithiasis, nightmares, nystagmus, oral candidiasis, orthostatic hypotension, ostealgia, osteoarthritis, osteoporosis, otalgia, otitis media, pancreatitis, pancytopenia, paralysis, paranoia, petechia, phlebitis, pneumonia, pneumothorax, polyuria, prolonged Q-T interval on ECG, psychomotor agitation, psychoneurosis, psychotic depression, pulmonary embolism, restless leg syndrome,	photosensitivity, Stevens-Johnson syndrome, stomatitis, suicidal ideation, syncope, tachycardia, tendinous contracture, tendonitis, tenosynovitis, thrombocytopenia, tonic-clonic seizures, twitching, ulcerative colitis, urinary incontinence, urinary urgency, urticaria, uterine fibroid enlargement, uterine hemorrhage, vaginal hemorrhage, varicose veins, ventricular premature contractions, vertigo, vesiculobullous dermatitis, voice disorder, weight loss, xeroderma, yawning					

Adverse Effect	Bupropion (%)	Mirtazapine (%)	Nefazodone (%)	Trazodone (%)	Vilazodone (%)	Vortioxetine (%)	Atomoxetine (%)	Lithium (%)
		rhabdomyolysis, rupture of tendon, seborrhea, sedation, seizure, serotonin syndrome, sialorrhea, skin hypertrophy, skin photosensitivity, Stevens-Johnson syndrome, stomatitis, stupor, suicidal behavior, suicidal ideation, syncope, tenosynovitis, thrombocytopenia, tongue discoloration, tongue edema, tonic-clonic seizures, torsades de pointes (rare), toxic epidermal necrolysis, ulcer, urethritis, urinary incontinence, urinary retention, urinary urgency, urticaria, uterine hemorrhage, vaginitis, vascular headache, ventricular fibrillation, ventricular premature contractions, ventricular tachycardia, weight loss, withdrawal syndrome, xeroderma						

Key: NR = not reported

Summary

Overall, each of the miscellaneous and serotonergic agents demonstrates efficacy in the treatment of labeled indications. Evidence supports the use of bupropion in the treatment of smoking cessation. Evidence supports the use of atomoxetine in the treatment of ADHD with efficacy similarly to methylphenidate. Evidence supports the use of lithium in bipolar disorder. Comparative trials among the miscellaneous serotonergic agents in the treatment of depression are limited and clinical evidence is insufficient to differentiate between agents. The miscellaneous serotonergic medications do differ in their adverse event profiles. Limited comparative evidence supports the safety and tolerability of the various agents. Individualization of therapy is recommended with consideration of the patient age, history, comorbidities, type and severity of mental disorder, underlying disease and concurrent medications.

References

1. Lexi-Drugs. Wolters Kluwer; 2015. http://online.lexi.com/lco/action/index/dataset/patch_f. Accessed 11/7/15.
2. Micromedex. Truven Health Analytics; 2015. http://micromedex.com/.
3. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; September 15, 2015.
4. Fitzpatrick L. A Brief History of Antidepressants. *Time.* 2010.
5. Rose N. Becoming Neurochemical Selves. In: Stehr N, ed. *Biotechnology: Between Commerce and Civil Society*. New Brunswick, NJ:: Transaction Publishers; 2004:90-91.
6. Glassman AH, Pardell R, Woodring S. Cardiovascular effects of the standard tricyclic antidepressants. *Clinical chemistry.* 1988;34(5):856-858.
7. LoVecchio F, Mattison E. Atypical and Serotonergic Antidepressants. . In: Tintinalli JE, Stapczynski J, Ma O, Yealy DM, Meckler GD, Cline DM, eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide* 8th ed. New York, NY McGraw-Hill; 2016.
8. O'Donnell JM, Shelton RC. Drug Therapy of Depression and Anxiety Disorders. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutic*. 12th ed. New York, NY: McGraw-Hill; 2011.
9. Lexi-Comp I, ed *Drug Information Handbook.* 21st ed. Hudson, OH: Lexi-Comp; 2016.
10. McEvoy GK, Snow EK, Kester L, Litvak K, Miller J, Welsh OH, eds. *AHFS 2016 Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2016.
11. CDC. Mental Health Surveillance. 2016; http://www.cdc.gov/mentalhealthsurveillance/fact_sheet.html. Accessed 03/18/2016.
12. Reus V. Mental Disorders. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 19 ed. New York, NY: McGraw-Hill; 2015.
13. CDC. Databreifs. 2016; http://www.cdc.gov/nchs/data/databriefs/db135.htm#x2013;2010</a. Accessed 03/18/2016.
14. NIH. Mood Disorder Statistics. 2016; http://www.nimh.nih.gov/health/statistics/prevalence/any-mood-disorder-among-adults.shtml. Accessed 03/18/2016.
15. ADAA. Facts and Statistics. 2016; http://www.adaa.org/about-adaa/press-room/facts-statistics. Accessed 03/18/2016.
16. CDC. Mental Health Basics. 2016; http://www.cdc.gov/mentalhealth/basics/burden.htm. Accessed 03/18/2016.
17. McDonagh MS, Peterson K, Carson S, Fu R, Thakurta S. Drug class review: Atypical Antipsychotic Drugs. Update 3. . In: University OHaS, ed2010.
18. Bauer M, Pfennig A, Severus E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry.* 2013;14(5):334-385.
19. American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder. (2010).
20. NICE. Guidelines for the management of Diabetes. 2009; http://pathways.nice.org.uk/pathways/diabetes#path=view%3A/pathways/diabetes/managing-type-2-diabetes.xml&content=view-index. Accessed 3/02/2015, 2015.
21. American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders 2007.

22. Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. *Canadian journal of psychiatry. Revue canadienne de psychiatrie.* 2010;55(3):126-135.
23. Institute for Clinical Systems Improvement (ICSI): Major Depression in Adults in Primary Care. 2011.
24. Kennedy DJ. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults 2009.
25. CDC. Bipolar Mental Health Basics. 2016; http://www.cdc.gov/mentalhealth/basics/mental-illness/bipolar.htm. Accessed 03/18/2016.
26. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Archives of general psychiatry.* 2011;68(3):241-251.
27. Safer DJ, Magno Zito J, Safer AM. Age-grouped differences in bipolar mania. *Comprehensive psychiatry.* 2012;53(8):1110-1117.
28. Messing RO, Nestler EJ. Biology of Psychiatric Disorders. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19e*. New York, NY: McGraw-Hill Education; 2015.
29. Ouanes S, Chennoufi L, Cheour M. An update on the treatment of mixed bipolar states: what is new in 2013? *Journal of affective disorders.* 2014;158:53-55.
30. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry.* 2010;11(2):81-109.
31. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry.* 2013;14(3):154-219.
32. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry.* 2009;10(2):85-116.
33. Searight H, Shinabarger C. Attention Deficit Hyperactivity Disorder. In: Feldman MD, Christensen JF, Satterfield JM, eds. *Behavioral Medicine: A Guide for Clinical Practice*. 4th ed. New York, NY: McGraw-Hill; 2014.
34. Kendall T, Morriss R, Mayo-Wilson E, Marcus E, Guideline Development Group of the National Institute for H, Care E. Assessment and management of bipolar disorder: summary of updated NICE guidance. *Bmj.* 2014;349:g5673.
35. McClellan J, Kowatch R, Findling RL, Work Group on Quality I. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2007;46(1):107-125.
36. Walsh JK, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. *Human Psychopharmacology.* 1998;13(3):191-198.
37. CDC. ADHD Key Findings. 2016; http://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html. Accessed 04/01/2016.
38. CDC. Attention Deficit Disorder. 2016; http://www.cdc.gov/ncbddd/adhd/data.html. Accessed 04/01/2016.
39. NIH. Attention Deficit Disorder Stats. 2016; http://www.nimh.nih.gov/health/statistics/prevalence/attention-deficit-hyperactivity-disorder-among-adults.shtml. Accessed 04/01/2016.

40. CDC. Medical conditions: Attention Deficit Disorder. 2016; http://www.cdc.gov/ncbddd/adhd/conditions.html. Accessed 04/01/2016.
41. CDC. ADHD Facts. 2016; http://www.cdc.gov/ncbddd/adhd/facts.html. Accessed 04/01/2016.
42. CDC. 2016; http://www.cdc.gov/ncbddd/adhd/diagnosis.html. Accessed 04/01/2016.
43. CDC. Teatment: ADHD. 2016; http://www.cdc.gov/ncbddd/adhd/treatment.html. Accessed 04/01/2016.
44. NIH. Health Topics: ADHD. 2016; http://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml, 04/01/2016.
45. Spencer T. Chapter 35. Attention-Deficit/Hyperactivity Disorder. In: Ebert MH, Loosen PT, Nurcombe B, Leckman JF, eds. *CURRENT Diagnosis & Treatment: Psychiatry*. 2nd ed. New York, NY: McGraw-Hill; 2008.
46. Pliszka S, Issues AWGoQ. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2007;46(7):894-921.
47. Pediatrics AAo. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/ Hyperactivity Disorder in Children and Adolescents. 2011.
48. Kendall T, Taylor E, Perez A, Taylor C, Guideline Development G. Diagnosis and management of attention-deficit/hyperactivity disorder in children, young people, and adults: summary of NICE guidance. *Bmj.* 2008;337:a1239.
49. Kollins SH, Jain R, Brams M, et al. Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. *Pediatrics.* 2011;127(6):e1406-1413.
50. Improvement IfCS. Health care guideline: diagnosis and management of attention deficit hyperactivity disorder in primary care for school-age children and adolescents. 9th ed. Bloomington (MN): Institute for Clinical Systems Improvement; 2012.
51. Today P. Seasonal Affective Disorder. 2015; https://www.psychologytoday.com/conditions/seasonal-affective-disorder. Accessed 5/16/2016.
52. Health NIoM. Seasonal Affective Disorder. 2016; http://www.nimh.nih.gov/health/topics/seasonal-affective-disorder/index.shtml. Accessed 5/16/16.
53. Health NIoM. Medline Plus: Seasonal Affective Disorder 2016; https://www.nlm.nih.gov/medlineplus/seasonalaffectivedisorder.html. Accessed 05/16/16.
54. Sanacora G. New understanding of mechanisms of action of bipolar medications. *The Journal of clinical psychiatry.* 2008;69 Suppl 5:22-27.
55. DeBattista C. Antipsychotic Agents & Lithium. In: Katzung BG, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 13th ed. New York, NY: McGraw-Hill; 2015.
56. DeBattista C. Antidepressant Agents. In: Katzung BG, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 13th ed. New York, NY: McGraw-Hill; 2015.
57. Flexner C. Antiretroviral Agents and the Treatment of HIV Infection. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. Ney York, NY: McGraw-Hill; 2011.
58. Avena-Woods C, Hilas O. Antidepressant use in underweight older adults. *The Consultant pharmacist : the journal of the American Society of Consultant Pharmacists.* 2012;27(12):868-870.
59. Banerjee S, Hellier J, Romeo R, et al. Study of the use of antidepressants for depression in dementia: the HTA-SADD trial--a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. *Health technology assessment (Winchester, England).* 2013;17(7):1-166.

60. Bech P. Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP).* 2001;4(4):337-345.
61. Biederman J, Spencer T, Wilens T. Evidence-based pharmacotherapy for attention-deficit hyperactivity disorder. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP).* 2004;7(1):77-97.
62. Biederman J, Spencer TJ, Newcorn JH, et al. Effect of comorbid symptoms of oppositional defiant disorder on responses to atomoxetine in children with ADHD: a meta-analysis of controlled clinical trial data. *Psychopharmacology.* 2007;190(1):31-41.
63. Blier P, Ward HE, Tremblay P, Laberge L, Hebert C, Bergeron R. Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. *The American journal of psychiatry.* 2010;167(3):281-288.
64. Bruijn JA, Moleman P, Mulder PG, van den Broek WW. Comparison of 2 treatment strategies for depressed inpatients: imipramine and lithium addition or mirtazapine and lithium addition. *The Journal of clinical psychiatry.* 1998;59(12):657-663.
65. Bushe CJ, Savill NC. Systematic review of atomoxetine data in childhood and adolescent attention-deficit hyperactivity disorder 2009-2011: focus on clinical efficacy and safety. *Journal of psychopharmacology (Oxford, England).* 2014;28(3):204-211.
66. Cheng JY, Chen RY, Ko JS, Ng EM. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. *Psychopharmacology.* 2007;194(2):197-209.
67. Khan A, Cutler AJ, Kajdasz DK, et al. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. *The Journal of clinical psychiatry.* 2011;72(4):441-447.
68. Khan A, Sambunaris A, Edwards J, Ruth A, Robinson DS. Vilazodone in the treatment of major depressive disorder: efficacy across symptoms and severity of depression. *International clinical psychopharmacology.* 2014;29(2):86-92.
69. Citrome L. Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *International journal of clinical practice.* 2014;68(1):60-82.
70. Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *International journal of clinical practice.* 2012;66(4):356-368.
71. Citrome L, Gommoll CP, Tang X, Nunez R, Mathews M. Evaluating the efficacy of vilazodone in achieving remission in patients with major depressive disorder: post-hoc analyses of a phase IV trial. *International clinical psychopharmacology.* 2015;30(2):75-81.
72. Clayton AH, Gommoll C, Chen D, Nunez R, Mathews M. Sexual dysfunction during treatment of major depressive disorder with vilazodone, citalopram, or placebo: results from a phase IV clinical trial. *International clinical psychopharmacology.* 2015;30(4):216-223.
73. Croft HA, Pomara N, Gommoll C, Chen D, Nunez R, Mathews M. Efficacy and safety of vilazodone in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *The Journal of clinical psychiatry.* 2014;75(11):e1291-1298.
74. Cyr M, Brown CS. Nefazodone: its place among antidepressants. *The Annals of pharmacotherapy.* 1996;30(9):1006-1012.

75. Durell T, Adler L, Wilens T, Paczkowski M, Schuh K. Atomoxetine treatment for ADHD: younger adults compared with older adults. *Journal of attention disorders.* 2010;13(4):401-406.
76. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *The American journal of psychiatry.* 2006;163(7):1161-1172.
77. Fu J, Chen Y. The efficacy and safety of 5 mg/d Vortioxetine compared to placebo for major depressive disorder: A meta-analysis. *Psychopharmacology.* 2015;232(1):7-16.
78. Gleason MM, Egger HL, Emslie GJ, et al. Psychopharmacological treatment for very young children: contexts and guidelines. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2007;46(12):1532-1572.
79. Guay DR. Vilazodone hydrochloride, a combined SSRI and 5-HT1A receptor agonist for major depressive disorder. *The Consultant pharmacist : the journal of the American Society of Consultant Pharmacists.* 2012;27(12):857-867.
80. Hirschfeld RM, Montgomery SA, Aguglia E, et al. Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. *The Journal of clinical psychiatry.* 2002;63(9):826-837.
81. Jain R, Chen D, Edwards J, Mathews M. Early and sustained improvement with vilazodone in adult patients with major depressive disorder: post hoc analyses of two phase III trials. *Current medical research and opinion.* 2014;30(2):263-270.
82. Jain R, Mahableshwarkar AR, Jacobsen PL, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP).* 2013;16(2):313-321.
83. Kasper S, Zivkov M, Roes KC, Pols AG. Pharmacological treatment of severely depressed patients: a meta-analysis comparing efficacy of mirtazapine and amitriptyline. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology.* 1997;7(2):115-124.
84. Lindsey WT. Vilazodone for the treatment of depression. *The Annals of pharmacotherapy.* 2011;45(7-8):946-953.
85. Magder DM, Aleksic I, Kennedy SH. Tolerability and efficacy of high-dose moclobemide alone and in combination with lithium and trazodone. *Journal of clinical psychopharmacology.* 2000;20(3):394-395.
86. Martinon-Torres G, Fioravanti M, Grimley EJ. Trazodone for agitation in dementia. *The Cochrane database of systematic reviews.* 2004(4):Cd004990.
87. Meeker AS, Herink MC, Haxby DG, Hartung DM. The safety and efficacy of vortioxetine for acute treatment of major depressive disorder: a systematic review and meta-analysis. *Systematic reviews.* 2015;4:21.
88. Montoya A, Quail D, Anand E, Cardo E, Alda JA, Escobar R. Prognostic factors of improvement in health-related quality of life in atomoxetine-treated children and adolescents with attention-deficit/hyperactivity disorder, based on a pooled analysis. *Attention deficit and hyperactivity disorders.* 2014;6(1):25-34.
89. Ostrow D. The new generation antidepressants: promising innovations or disappointments? *The Journal of clinical psychiatry.* 1985;46(10 Pt 2):25-31.
90. Pearce EF, Murphy JA. Vortioxetine for the treatment of depression. *The Annals of pharmacotherapy.* 2014;48(6):758-765.

91. Perwien AR, Faries DE, Kratochvil CJ, Sumner CR, Kelsey DK, Allen AJ. Improvement in health-related quality of life in children with ADHD: an analysis of placebo controlled studies of atomoxetine. *Journal of developmental and behavioral pediatrics : JDBP.* 2004;25(4):264-271.
92. Price LH, Charney DS, Heninger GR. Efficacy of lithium-tranylcypromine treatment in refractory depression. *The American journal of psychiatry.* 1985;142(5):619-623.
93. Robinson DS, Kajdasz DK, Gallipoli S, Whalen H, Wamil A, Reed CR. A 1-year, open-label study assessing the safety and tolerability of vilazodone in patients with major depressive disorder. *Journal of clinical psychopharmacology.* 2011;31(5):643-646.
94. Rudorfer MV, Golden RN, Potter WZ. Second-generation antidepressants. *The Psychiatric clinics of North America.* 1984;7(3):519-534.
95. Sung SC, Haley CL, Wisniewski SR, et al. The impact of chronic depression on acute and long-term outcomes in a randomized trial comparing selective serotonin reuptake inhibitor monotherapy versus each of 2 different antidepressant medication combinations. *The Journal of clinical psychiatry.* 2012;73(7):967-976.
96. Szegedi A, Jansen WT, van Willigenburg AP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *The Journal of clinical psychiatry.* 2009;70(3):344-353.
97. Thase ME, Nierenberg AA, Vrijland P, van Oers HJ, Schutte AJ, Simmons JH. Remission with mirtazapine and selective serotonin reuptake inhibitors: a meta-analysis of individual patient data from 15 controlled trials of acute phase treatment of major depression. *International clinical psychopharmacology.* 2010;25(4):189-198.
98. Vidal C, Reese C, Fischer BA, Chiapelli J, Himelhoch S. Meta-Analysis of Efficacy of Mirtazapine as an Adjunctive Treatment of Negative Symptoms in Schizophrenia. *Clinical schizophrenia & related psychoses.* 2015;9(2):88-95.
99. Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. A review of current evidence for vilazodone in major depressive disorder. *International journal of psychiatry in clinical practice.* 2013;17(3):160-169.
100. Watanabe N, Omori IM, Nakagawa A, et al. Mirtazapine versus other antidepressive agents for depression. *The Cochrane database of systematic reviews.* 2011(12):Cd006528.
101. Watanabe N, Omori IM, Nakagawa A, et al. Mirtazapine versus other antidepressants in the acute-phase treatment of adults with major depression: systematic review and meta-analysis. *The Journal of clinical psychiatry.* 2008;69(9):1404-1415.
102. Whyte EM, Basinski J, Farhi P, et al. Geriatric depression treatment in nonresponders to selective serotonin reuptake inhibitors. *The Journal of clinical psychiatry.* 2004;65(12):1634-1641.
103. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2013 reviews. *Addiction.* 2014;109(9):1414-1425.
104. de Vries C, van Bergen A, Regeer EJ, Benthem E, Kupka RW, Boks MP. The effectiveness of restarted lithium treatment after discontinuation: reviewing the evidence for discontinuation-induced refractoriness. *Bipolar disorders.* 2013;15(6):645-649.
105. Gillman PK. A systematic review of the serotonergic effects of mirtazapine in humans: implications for its dual action status. *Hum Psychopharmacol.* 2006;21(2):117-125.
106. Pehrson AL, Sanchez C. Altered gamma-aminobutyric acid neurotransmission in major depressive disorder: a critical review of the supporting evidence and the influence of serotonergic antidepressants. *Drug design, development and therapy.* 2015;9:603-624.
107. Polanczyk G, Bigarella MP, Hutz MH, Rohde LA. Pharmacogenetic approach for a better drug treatment in children. *Current pharmaceutical design.* 2010;16(22):2462-2473.

108. Sitsen JM, Voortman G, Timmer CJ. Pharmacokinetics of mirtazapine and lithium in healthy male subjects. *Journal of psychopharmacology (Oxford, England).* 2000;14(2):172-176.
109. Theunissen EL, Street D, Hojer AM, Vermeeren A, van Oers A, Ramaekers JG. A randomized trial on the acute and steady-state effects of a new antidepressant, vortioxetine (Lu AA21004), on actual driving and cognition. *Clin Pharmacol Ther.* 2013;93(6):493-501.
110. Bangs ME, Tauscher-Wisniewski S, Polzer J, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2008;47(2):209-218.
111. Bangs ME, Wietecha LA, Wang S, Buchanan AS, Kelsey DK. Meta-analysis of suicide-related behavior or ideation in child, adolescent, and adult patients treated with atomoxetine. *Journal of child and adolescent psychopharmacology.* 2014;24(8):426-434.
112. Barkla XM, McArdle PA, Newbury-Birch D. Are there any potentially dangerous pharmacological effects of combining ADHD medication with alcohol and drugs of abuse? A systematic review of the literature. *BMC psychiatry.* 2015;15:270.
113. Camporeale A, Day KA, Ruff D, Arsenault J, Williams D, Kelsey DK. Profile of sexual and genitourinary treatment-emergent adverse events associated with atomoxetine treatment: a pooled analysis. *Drug safety.* 2013;36(8):663-671.
114. Clayton AH, Kennedy SH, Edwards JB, Gallipoli S, Reed CR. The effect of vilazodone on sexual function during the treatment of major depressive disorder. *The journal of sexual medicine.* 2013;10(10):2465-2476.
115. Duong S, Chung K, Wigal SB. Metabolic, toxicological, and safety considerations for drugs used to treat ADHD. *Expert opinion on drug metabolism & toxicology.* 2012;8(5):543-552.
116. Eiland LS, Bell EA, Erramouspe J. Priapism associated with the use of stimulant medications and atomoxetine for attention-deficit/hyperactivity disorder in children. *The Annals of pharmacotherapy.* 2014;48(10):1350-1355.
117. Einarson A, Bonari L, Voyer-Lavigne S, et al. A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Canadian journal of psychiatry. Revue canadienne de psychiatrie.* 2003;48(2):106-110.
118. Martinez MA, Ballesteros S, Sanchez de la Torre C, Almarza E. Investigation of a fatality due to trazodone poisoning: case report and literature review. *Journal of analytical toxicology.* 2005;29(4):262-268.
119. Polzer J, Bangs ME, Zhang S, et al. Meta-analysis of aggression or hostility events in randomized, controlled clinical trials of atomoxetine for ADHD. *Biological psychiatry.* 2007;61(5):713-719.
120. Watanabe N, Omori IM, Nakagawa A, et al. Safety reporting and adverse-event profile of mirtazapine described in randomized controlled trials in comparison with other classes of antidepressants in the acute-phase treatment of adults with depression: systematic review and meta-analysis. *CNS drugs.* 2010;24(1):35-53.
121. Zisook S, Lesser IM, Lebowitz B, et al. Effect of antidepressant medication treatment on suicidal ideation and behavior in a randomized trial: an exploratory report from the Combining Medications to Enhance Depression Outcomes Study. *The Journal of clinical psychiatry.* 2011;72(10):1322-1332.
122. Dolder CR, Nelson MH, Iler CA. The effects of mirtazapine on sleep in patients with major depressive disorder. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists.* 2012;24(3):215-224.
123. Taylor S, Harley C, Takeuchi E, Brown J, Velikova G. Detecting and discussing sexual problems during chemotherapy for breast cancer. *The breast journal.* 2013;19(5):566-567.
124. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet (London, England).* 2012;379(9817):721-728.

125. Areberg J, Petersen KB, Chen G, Naik H. Population pharmacokinetic meta-analysis of vortioxetine in healthy individuals. *Basic & clinical pharmacology & toxicology.* 2014;115(6):552-559.
126. Boinpally R, Alcorn H, Adams MH, Longstreth J, Edwards J. Pharmacokinetics of vilazodone in patients with mild or moderate renal impairment. *Clinical drug investigation.* 2013;33(3):199-206.
127. Boinpally R, Gad N, Gupta S, Periclou A. Influence of CYP3A4 induction/inhibition on the pharmacokinetics of vilazodone in healthy subjects. *Clinical therapeutics.* 2014;36(11):1638-1649.
128. Chen G, Lee R, Hojer AM, Buchbjerg JK, Serenko M, Zhao Z. Pharmacokinetic drug interactions involving vortioxetine (Lu AA21004), a multimodal antidepressant. *Clinical drug investigation.* 2013;33(10):727-736.
129. Edwards J, Sperry V, Adams MH, et al. Vilazodone lacks proarrhythmogenic potential in healthy participants: a thorough ECG study. *International journal of clinical pharmacology and therapeutics.* 2013;51(6):456-465.
130. Murck H, Frieboes RM, Antonijevic IA, Steiger A. Distinct temporal pattern of the effects of the combined serotonin-reuptake inhibitor and 5-HT1A agonist EMD 68843 on the sleep EEG in healthy men. *Psychopharmacology.* 2001;155(2):187-192.
131. Rickels K, Athanasiou M, Robinson DS, Gibertini M, Whalen H, Reed CR. Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. *The Journal of clinical psychiatry.* 2009;70(3):326-333.
132. Sasada K, Iwamoto K, Kawano N, et al. Effects of repeated dosing with mirtazapine, trazodone, or placebo on driving performance and cognitive function in healthy volunteers. *Hum Psychopharmacol.* 2013;28(3):281-286.
133. Ware JC, Rose FV, McBrayer RH. The acute effects of nefazodone, trazodone and buspirone on sleep and sleep-related penile tumescence in normal subjects. *Sleep.* 1994;17(6):544-550.
134. Baldo P, Doree C, Molin P, McFerran D, Cecco S. Antidepressants for patients with tinnitus. *The Cochrane database of systematic reviews.* 2012;9:Cd003853.
135. Becker ME, Hertzberg MA, Moore SD, Dennis MF, Bukenya DS, Beckham JC. A placebo-controlled trial of bupropion SR in the treatment of chronic posttraumatic stress disorder. *Journal of clinical psychopharmacology.* 2007;27(2):193-197.
136. Carpenter KM, McDowell D, Brooks DJ, Cheng WY, Levin FR. A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2009;18(1):53-64.
137. Dougall D, Poole N, Agrawal N. Pharmacotherapy for chronic cognitive impairment in traumatic brain injury. *The Cochrane database of systematic reviews.* 2015;12:Cd009221.
138. El-Chammas K, Keyes J, Thompson N, Vijayakumar J, Becher D, Jackson JL. Pharmacologic treatment of pediatric headaches: a meta-analysis. *JAMA pediatrics.* 2013;167(3):250-258.
139. Fawcett J, Barkin RL. A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. *The Journal of clinical psychiatry.* 1998;59(3):123-127.
140. Fawcett J, Marcus RN, Anton SF, O'Brien K, Schwiderski U. Response of anxiety and agitation symptoms during nefazodone treatment of major depression. *The Journal of clinical psychiatry.* 1995;56 Suppl 6:37-42.
141. Fink HA, MacDonald R, Rutks IR, Wilt TJ. Trazodone for erectile dysfunction: a systematic review and meta-analysis. *BJU international.* 2003;92(4):441-446.

142. Gartlehner G, Hansen RA, Carey TS, Lohr KN, Gaynes BN, Randolph LC. Discontinuation rates for selective serotonin reuptake inhibitors and other second-generation antidepressants in outpatients with major depressive disorder: a systematic review and meta-analysis. *International clinical psychopharmacology.* 2005;20(2):59-69.
143. Gommoll C, Durgam S, Mathews M, et al. A double-blind, randomized, placebo-controlled, fixed-dose phase III study of vilazodone in patients with generalized anxiety disorder. *Depression and anxiety.* 2015;32(6):451-459.
144. Kelwala S, Stanley M, Gershon S. History of antidepressants: successes and failures. *The Journal of clinical psychiatry.* 1983;44(5 Pt 2):40-48.
145. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. *The Journal of clinical psychiatry.* 2005;66(4):469-476.
146. Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant-associated insomnia. *The American journal of psychiatry.* 1994;151(7):1069-1072.
147. Phan SV, Kreys TJ. Adjunct mirtazapine for negative symptoms of schizophrenia. *Pharmacotherapy.* 2011;31(10):1017-1030.
148. Pope HG, Jr., Hudson JI. Antidepressant drug therapy for bulimia: current status. *The Journal of clinical psychiatry.* 1986;47(7):339-345.
149. Schoedel KA, Meier D, Chakraborty B, Manniche PM, Sellers EM. Subjective and objective effects of the novel triple reuptake inhibitor tesofensine in recreational stimulant users. *Clinical pharmacology and therapeutics.* 2010;88(1):69-78.
150. Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P. Antidepressants for agitation and psychosis in dementia. *The Cochrane database of systematic reviews.* 2011(2):Cd008191.
151. Somaini L, Donnini C, Raggi MA, et al. Promising medications for cocaine dependence treatment. *Recent patents on CNS drug discovery.* 2011;6(2):146-160.
152. Shoptaw SJ, Kao U, Heinzerling K, Ling W. Treatment for amphetamine withdrawal. *The Cochrane database of systematic reviews.* 2009(2):CD003021.
153. Mason M, Welsh EJ, Smith I. Drug therapy for obstructive sleep apnoea in adults. *The Cochrane database of systematic reviews.* 2013;5:CD003002.
154. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. *Drugs.* 1999;57(4):607-631.
155. McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in Alzheimer's disease. *The Cochrane database of systematic reviews.* 2014;3:Cd009178.
156. Bacaltchuk J, Hay P. Antidepressants versus placebo for people with bulimia nervosa. *The Cochrane database of systematic reviews.* 2003(4):CD003391.
157. Deshpande AV, Caldwell PH, Sureshkumar P. Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics). *The Cochrane database of systematic reviews.* 2012;12:CD002238.
158. Kessler L, Palla J, Baru JS, Onyenwenyi C, George AM, Lucas BP. Lithium as an adjunct to radioactive iodine for the treatment of hyperthyroidism: a systematic review and meta-analysis. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2014;20(7):737-745.
159. Edwards SJ, Hamilton V, Nherera L, Trevor N. Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: a systematic review and economic evaluation. *Health technology assessment (Winchester, England).* 2013;17(54):1-190.
160. McDonagh MS, Christensen V, Peterson K, Thakurta S. Drug Class Review: Pharmacological Treatments for Attention Deficit Hyperactivity Disorder. Update 3.: Oregon Health and Science University; 2009.

161. Pringsheim T, Steeves T. Pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children with comorbid tic disorders. *The Cochrane database of systematic reviews.* 2011(4):CD007990.
162. Cunill R, Castells X, Tobias A, Capella D. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. *Pharmacoepidemiol Drug Saf.* 2013;22(9):961-969.
163. Fredriksen M, Halmoy A, Faraone SV, Haavik J. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: a review of controlled and naturalistic studies. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology.* 2013;23(6):508-527.
164. Schwartz S, Correll CU. Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: results from a comprehensive meta-analysis and metaregression. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2014;53(2):174-187.
165. Roskell NS, Setyawan J, Zimovetz EA, Hodgkins P. Systematic evidence synthesis of treatments for ADHD in children and adolescents: indirect treatment comparisons of lisdexamfetamine with methylphenidate and atomoxetine. *Curr Med Res Opin.* 2014;30(8):1673-1685.
166. Stuhec M, Munda B, Svab V, Locatelli I. Comparative efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion and methylphenidate in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis with focus on bupropion. *Journal of affective disorders.* 2015;178:149-159.
167. Gartlehner G, Nussbaumer B, Gaynes BN, et al. Second-generation antidepressants for preventing seasonal affective disorder in adults. *The Cochrane database of systematic reviews.* 2015;11:CD011268.
168. Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *The Cochrane database of systematic reviews.* 2015;12:CD010078.
169. Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *The Cochrane database of systematic reviews.* 2013;2:CD007253.
170. Ebbert JO, Elrashidi MY, Stead LF. Interventions for smokeless tobacco use cessation. *The Cochrane database of systematic reviews.* 2015;10:CD004306.
171. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *The Cochrane database of systematic reviews.* 2014;1:CD000031.
172. Maziak W, Jawad M, Jawad S, Ward KD, Eissenberg T, Asfar T. Interventions for waterpipe smoking cessation. *The Cochrane database of systematic reviews.* 2015;7:CD005549.
173. Jawad M, Jawad S, Waziry RK, Ballout RA, Akl EA. Interventions for waterpipe tobacco smoking prevention and cessation: a systematic review. *Scientific reports.* 2016;6:25872.
174. Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation in Adults, Including Pregnant Women: A Review of Reviews for the U.S. Preventive Services Task Force. *Annals of internal medicine.* 2015;163(8):608-621.
175. Weiner E, Ball MP, Buchholz AS, et al. Bupropion sustained release added to group support for smoking cessation in schizophrenia: a new randomized trial and a meta-analysis. *The Journal of clinical psychiatry.* 2012;73(1):95-102.
176. Maneeton N, Maneeton B, Eurviriyanukul K, Srisurapanont M. Efficacy, tolerability, and acceptability of bupropion for major depressive disorder: a meta-analysis of randomized-controlled trials comparison with venlafaxine. *Drug design, development and therapy.* 2013;7:1053-1062.

177. Papakostas GI, Montgomery SA, Thase ME, Katz JR, Krishen A, Tucker VL. Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. *The Journal of clinical psychiatry.* 2007;68(12):1907-1912.
178. Papakostas GI, Stahl SM, Krishen A, et al. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of major depressive disorder with high levels of anxiety (anxious depression): a pooled analysis of 10 studies. *The Journal of clinical psychiatry.* 2008;69(8):1287-1292.
179. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biological psychiatry.* 2008;63(7):699-704.
180. Moriyama TS, Polanczyk GV, Terzi FS, Faria KM, Rohde LA. Psychopharmacology and psychotherapy for the treatment of adults with ADHD-a systematic review of available meta-analyses. *CNS Spectr.* 2013;18(6):296-306.
181. Weisler RH, Johnston JA, Lineberry CG, Samara B, Branconnier RJ, Billow AA. Comparison of bupropion and trazodone for the treatment of major depression. *Journal of clinical psychopharmacology.* 1994;14(3):170-179.
182. Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. *The Cochrane database of systematic reviews.* 2001(3):Cd003013.
183. Cipriani A, Smith K, Burgess S, Carney S, Goodwin G, Geddes J. Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. *The Cochrane database of systematic reviews.* 2006(4):CD003492.
184. Leucht S, McGrath J, Kissling W. Lithium for schizophrenia. *The Cochrane database of systematic reviews.* 2003(3):Cd003834.
185. Severus E, Taylor MJ, Sauer C, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *International journal of bipolar disorders.* 2014;2:15.
186. Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. *Pharmacopsychiatry.* 2014;47(2):43-52.
187. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *The American journal of psychiatry.* 2005;162(10):1805-1819.
188. Nelson JC, Baumann P, Delucchi K, Joffe R, Katona C. A systematic review and meta-analysis of lithium augmentation of tricyclic and second generation antidepressants in major depression. *Journal of affective disorders.* 2014;168:269-275.
189. Papakostas GI, Homberger CH, Fava M. A meta-analysis of clinical trials comparing mirtazapine with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. *Journal of psychopharmacology (Oxford, England).* 2008;22(8):843-848.
190. Alam A, Voronovich Z, Carley JA. A review of therapeutic uses of mirtazapine in psychiatric and medical conditions. *The primary care companion for CNS disorders.* 2013;15(5).
191. Hieber R, Dellenbaugh T, Nelson LA. Role of mirtazapine in the treatment of antipsychotic-induced akathisia. *The Annals of pharmacotherapy.* 2008;42(6):841-846.
192. van Moffaert M, de Wilde J, Vereecken A, et al. Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. *International clinical psychopharmacology.* 1995;10(1):3-9.
193. Papakostas GI, Fava M. A meta-analysis of clinical trials comparing the serotonin (5HT)-2 receptor antagonists trazodone and nefazodone with selective serotonin reuptake inhibitors for

the treatment of major depressive disorder. *European psychiatry : the journal of the Association of European Psychiatrists.* 2007;22(7):444-447.
194. Patten SB. The comparative efficacy of trazodone and imipramine in the treatment of depression. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 1992;146(7):1177-1182.
195. Workman EA, Short DD. Atypical antidepressants versus imipramine in the treatment of major depression: a meta-analysis. *The Journal of clinical psychiatry.* 1993;54(1):5-12.
196. Kolla BP, Mansukhani MP, Schneekloth T. Pharmacological treatment of insomnia in alcohol recovery: a systematic review. *Alcohol and alcoholism (Oxford, Oxfordshire).* 2011;46(5):578-585.
197. Pae CU, Wang SM, Han C, et al. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. *Journal of psychiatry & neuroscience : JPN.* 2015;40(3):174-186.
198. Pae CU, Wang SM, Han C, et al. Vortioxetine, a multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. *Journal of psychiatric research.* 2015;64:88-98.
199. Berhan A, Barker A. Vortioxetine in the treatment of adult patients with major depressive disorder: a meta-analysis of randomized double-blind controlled trials. *BMC psychiatry.* 2014;14:276.
200. Dittmann RW, Cardo E, Nagy P, et al. Efficacy and safety of lisdexamfetamine dimesylate and atomoxetine in the treatment of attention-deficit/hyperactivity disorder: a head-to-head, randomized, double-blind, phase IIIb study. *CNS drugs.* 2013;27(12):1081-1092.
201. Reed VA, Buitelaar JK, Anand E, et al. The Safety of Atomoxetine for the Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: A Comprehensive Review of Over a Decade of Research. *CNS drugs.* 2016;30(7):603-628.
202. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews.* 2013(5).
203. Belson MG, Kelley TR. Bupropion exposures: clinical manifestations and medical outcome. *The Journal of emergency medicine.* 2002;23(3):223-230.
204. Chun-Fai-Chan B, Koren G, Fayez I, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *American journal of obstetrics and gynecology.* 2005;192(3):932-936.
205. Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. *Cochrane Database of Systematic Reviews.* 2013(10).
206. Baldwin DS, Hawley CJ, Mellors K. A randomized, double-blind controlled comparison of nefazodone and paroxetine in the treatment of depression: safety, tolerability and efficacy in continuation phase treatment. *Journal of psychopharmacology (Oxford, England).* 2001;15(3):161-165.
207. FDA. Serzone (Nefazodone HCL). 2002; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154517.htm. Accessed 7/18, 2016.
208. Dunner DL, Laird LK, Zajecka J, Bailey L, Sussman N, Seabolt JL. Six-year perspectives on the safety and tolerability of nefazodone. *The Journal of clinical psychiatry.* 2002;63 Suppl 1:32-41.
209. Rhian McNaughton GH, Saad Shakir. An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making *BMJ Open 2014;4:1 e004221 doi:10.1136/bmjopen-2013-004221*

210. LiverTox: Nefazodone. 2016; https://livertox.nlm.nih.gov/Nefazodone.htm. Accessed 7/18, 2016.
211. Fagiolini A, Comandini A, Dell'Osso MC, Kasper S. Rediscovering Trazodone for the Treatment of Major Depressive Disorder. *CNS drugs.* 2012;26(12):1033-1049.
212. Laughren TP, Gobburu J, Temple RJ, et al. Vilazodone: clinical basis for the US Food and Drug Administration's approval of a new antidepressant. *The Journal of clinical psychiatry.* 2011;72(9):1166-1173.
213. Baldwin DS, Serenko M, Palo W, Lophaven S, Matz J. The safety and tolerability of vortioxetine (Lu AA21004) in the treatment of adults with major depressive disorder (MDD): A pooled analysis. *International Journal of Psychiatry in Clinical Practice.* 2013;17:16-17.